CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215430Orig1s000

PRODUCT QUALITY REVIEW(S)

Table of Contents

U.S. FOOD & DRUG ADMINISTRATION

RECOMMENDATION

☒ Approval
☐ Approval with Post-Marketing Commitment
☐ Complete Response

NDA # 215430
Assessment # 1 addendum 2

Drug Product Name	AXS-05 (dextromethorphan-bupropion)
Dosage Form	tablet
Strength	45 mg (dextromethorphan HBr) / 105 mg (bupropion HCl)
Route of Administration	oral
Rx/OTC Dispensed	Rx
Applicant	Axsome Therapeutics, Inc.
US agent, if applicable	N/A

Submission(s) Assessed	Document Date	Discipline(s) Affected
Supporting document 1; eCTD 0001	22 Feb 21	All, original submission
Supporting document 10; eCTD 0010	2 Apr 21	Drug product, process/facilities, biopharmaceutics
Supporting document 15; eCTD 0015	7 Jun 21	Process/facilities
Supporting document 18; eCTD 0018	24 Jun 21	Biopharmaceutics
Supporting document 19; eCTD 0019	30 Jun 21	Biopharmaceutics
Supporting document 21; eCTD 0021	2 Jul 21	Process/facilities
Supporting document 26; eCTD 0026	29 Dec 21	Drug product and biopharm
Supporting document 29; eCTD 0029	**6 Apr 22**	**Drug product – reviewed in this addendum**
Supporting document 30; eCTD 0030	**11 Apr 22**	**Drug product – reviewed in this addendum**

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessment	Secondary Assessment

Drug Substance	Gaetan Ladouceur	Donna Christner
Drug Product	Renish Delvadia	Julia Pinto
Manufacturing	Teng (Daisy) Xu	Sharmista Chatterjee
Microbiology	N/A	N/A
Biopharmaceutics	Kalpana Paudel	Ta-Chen Wu
Regulatory Business Process Manager	Teshara Bouie	
Application Technical Lead	Valerie Amspacher	
Laboratory (OTR)	N/A	N/A
Environmental	Renish Delvadia	Julia Pinto

EXECUTIVE SUMMARY

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

CMC recommends approval for this application. As stated in the CMC IQA addendum 1 dated 23 Mar 2022, Biopharm will have a PMC. The purpose of this second addendum is to review additional information submitted to the application in response to information requests about the level of the excipient cysteine hydrochloride and the acceptance criteria in the specification for bupropion impurity (b) (4) See Addendum 1 dated 23 Mar 2022 for PMC details.

A 6 month shelf-life is acceptable when stored at 25˚C.

See also original CMC review submitted in Panorama and DARRTS 19 Jul 2021 as well as addendum 1 dated 23 Mar 2022.

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

AXS-05 is an oral, fixed-dose, combination of dextromethorphan hydrobromide (HBr) and bupropion hydrochloride (HCl). AXS-05 is formulated into round, beige film-coated bilayer tablets. The bupropion HCl in the tablets is formulated for extended release, and the dextromethorphan HBr is formulated for immediate release. The commercial drug product will be debossed on one side with “45/105” and will be plain on the other side.

A 6 month shelf-life is acceptable when stored at 25˚C.

See also original CMC review submitted in Panorama and DARRTS 19 Jul 2021 as well as addendum 1 dated 23 Mar 2022.

Proposed Indication(s) including Intended Patient Population	Treatment of Major Depressive Disorder
Duration of Treatment	chronic
Maximum Daily Dose	Dextromethorphan 90 mg; bupropion 210 mg
Alternative Methods of Administration	N/A

B. Quality Assessment Overview

Drug Substance: Adequate

See original CMC review submitted in Panorama and DARRTS 19 Jul 2021.

Drug Product: Adequate

When the original CMC IQA (dated 19 Jul 2021 in Panorama and DARRTS) was completed there were two outstanding pharm/tox issues:
1.Was the specification for bupropion impurity (b)(4) acceptable?
2.Was the level of the excipient cysteine hydrochloride acceptable?
Pharm/tox has made decisions on these issues and this addendum captures those pharm/tox determinations. See the drug product review in this document for details on those decisions.

See also original CMC review submitted in Panorama and DARRTS 19 Jul 2021 as well as addendum 1 dated 23 Mar 2022.

Labeling: Adequate

See original CMC review submitted in Panorama and DARRTS 19 Jul 2021.

Manufacturing: Adequate

See original CMC review submitted in Panorama and DARRTS 19 Jul 2021.

Biopharmaceutics: Adequate

See also original CMC review submitted in Panorama and DARRTS 19 Jul 2021 as well as addendum 1 dated 23 Mar 2022.

Microbiology (if applicable): Choose an item.

N/A

C. Risk Assessment

From Initial Risk Identification			Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations / Comments**
		H, M, or L		Acceptable or Not Acceptable	
Assay, Stability	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipments • Site	L	Controlled by specification	Acceptable	
Physical stability (solid state) (dextromethorpan is considered BCS II and bupropion is BCS I)	• Formulation • Raw materials • Process parameters • Scale/equipments • Site	L/M	Controlled by specification	Acceptable	
Content uniformity	• Formulation • Raw materials • Process parameters • Scale/equipments • Site	M	Controlled by specification	Acceptable	
Microbial limits	• Formulation • Raw materials • Process parameters • Scale/equipments • Site	L	Controlled by specification	Acceptable	
Dissolution – BCS Class I & III (bupropion is BCS I)	• Formulation • Raw materials • Process parameters • Scale/equipments • Site	L	Controlled by specification	Acceptable (with PMC)	

Dissolution – BCS Class II & IV (dextromethorphan is considered BCS II)	• Formulation • Raw materials • Exclude major reformulations • Process parameters • Scale/equipments • Site	M	Controlled by specification	Acceptable (with PMC)	
Delamination (for multilayered tablets only)	• Formulation • Process parameters • Scale/equipments • Site	L	Controlled by specification	Acceptable	
Alcohol dose dumping	• Formulation • Process parameters • Scale/equipments • Site	H	See original review and information added to labeling	Acceptable	

D. List of Deficiencies for Complete Response

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

2. Drug Substance Deficiencies

3. Drug Product Deficiencies

4. Labeling Deficiencies

5. Manufacturing Deficiencies

6. Biopharmaceutics Deficiencies

7. Microbiology Deficiencies

8. Other Deficiencies (Specify discipline, such as Environmental)

QUALITY ASSESSMENT DATA SHEET

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Comments
(b) (4)	II		(b) (4)	1	13 Apr 20	Reviewed by Siba Bhattacharyya
	II			1	21 Jan 21	Reviewed by Steven Kinsley
	III			4		
	III			4		
	III			4		

Action codes for DMF Table:
1 – DMF Reviewed.
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

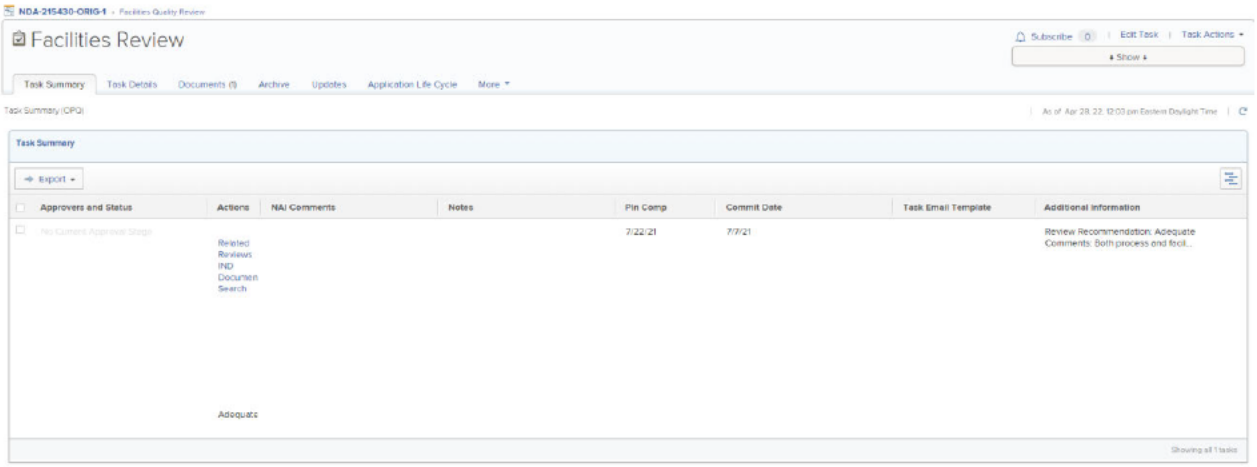
B. OTHER DOCUMENTS: *IND, RLD, RS, Approved NDA*

Document	Application Number	Description
IND	124813	
NDA	021879	Nuedexta (dextromethorphan hydrobromide / quinidine sulfate) capsules
NDA	020358	Wellbutrin SR (bupropion hydrochloride) sustained-release tablets

2. CONSULTS

Discipline	Status	Recommendation	Date	Assessor
Biostatistics				
Pharmacology/Toxicology				
CDRH-ODE				
CDRH-OC				
Clinical				
Other				

Panorama screenshot showing approval of facilities (taken 28 Apr 2022)



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/s/

VALERIE R AMSPACHER
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Table of Contents

U.S. FOOD & DRUG ADMINISTRATION

RECOMMENDATION

☒ Approval
☐ Approval with Post-Marketing Commitment
☐ Complete Response

NDA # 215430
Assessment # 1 addendum

Drug Product Name	AXS-05 (dextromethorphan-bupropion)
Dosage Form	tablet
Strength	45 mg (dextromethorphan HBr) / 105 mg (bupropion HCl)
Route of Administration	oral
Rx/OTC Dispensed	Rx
Applicant	Axsome Therapeutics, Inc.
US agent, if applicable	N/A

Submission(s) Assessed	Document Date	Discipline(s) Affected
Supporting document 1; eCTD 0001	22 Feb 21	All, original submission
Supporting document 10; eCTD 0010	2 Apr 21	Drug product, process/facilities, biopharmaceutics
Supporting document 15; eCTD 0015	7 Jun 21	Process/facilities
Supporting document 18; eCTD 0018	24 Jun 21	Biopharmaceutics
Supporting document 19; eCTD 0019	30 Jun 21	Biopharmaceutics
Supporting document 21; eCTD 0021	2 Jul 21	Process/facilities
Supporting document 26; eCTD 0026	**29 Dec 21**	**Drug product and biopharm; this is the only submission reviewed in this addendum**

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessment	Secondary Assessment
Drug Substance	Gaetan Ladouceur	Donna Christner
Drug Product	Renish Delvadia	Julia Pinto
Manufacturing	Teng (Daisy) Xu	Sharmista Chatterjee

Microbiology	N/A	N/A
Biopharmaceutics	Kalpana Paudel	Ta-Chen Wu
Regulatory Business Process Manager	Teshara Bouie	
Application Technical Lead	Valerie Amspacher	
Laboratory (OTR)	N/A	N/A
Environmental	Renish Delvadia	Julia Pinto

EXECUTIVE SUMMARY

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

CMC recommends approval for this application. Biopharm will have a PMC. The purpose of this addendum is to review additional information submitted to the application in response to a Discipline Review Letter sent 22 Oct 21. Drug product and biopharmaceutics reviewed additional information received on 29 Dec 21 as Supporting Document 26; eCTD 0026 and now recommend approval for this NDA.

A 6 month shelf-life is acceptable when stored at 25˚C.

See also original CMC review submitted in Panorama and DARRTS 19 Jul 2021. This addendum resolves the comments listed as deficiencies in the original CMC review.

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

AXS-05 is an oral, fixed-dose, combination of dextromethorphan hydrobromide (HBr) and bupropion hydrochloride (HCl). AXS-05 is formulated into round, beige film-coated bilayer tablets. The bupropion HCl in the tablets is formulated for extended release, and the dextromethorphan HBr is formulated for immediate release. The commercial drug product will be debossed on one side with “45/105” and will be plain on the other side.

A 6 month shelf-life is acceptable when stored at 25˚C.

See also original CMC review submitted in Panorama and DARRTS 19 Jul 2021. This addendum resolves the comments listed as deficiencies in the original CMC review.

Proposed Indication(s) including Intended Patient Population	Treatment of Major Depressive Disorder
Duration of Treatment	chronic
Maximum Daily Dose	Dextromethorphan 90 mg; bupropion 210 mg
Alternative Methods of Administration	N/A

B. Quality Assessment Overview

Drug Substance: Adequate

See original CMC review submitted in Panorama and DARRTS 19 Jul 2021.

Drug Product: Adequate

The analytical method CTMLP 3898 has been revalidated to lower the limit of quantitation (LOQ) to (b) (4)% for known bupropion HCl related compounds ((b) (4)), bupropion HCl unknown related compounds. LOQ for dextromethorphan HBr unknown related compounds is also (b) (4)% for the proposed commercial strength. Additionally, the method CTMLP 4006 has been revalidated by the Applicant to lower the LOQ to (b) (4)% for known bupropion HCl related compounds, (b) (4) and (b) (4) The revised LOQ value of (b) (4)% for degradation products in the proposed commercial drug product strength is acceptable.

Labeling: Adequate

See original CMC review submitted in Panorama and DARRTS 19 Jul 2021.

Manufacturing: Adequate

See original CMC review submitted in Panorama and DARRTS 19 Jul 2021.

Biopharmaceutics: Adequate

The Applicant submitted two separate dissolution methods for each component of the proposed drug product. These new methods are CTMLP 5319 (Dissolution Release of Dextromethorphan) and CTMLP 5320 (Dissolution Release of Bupropion HCl). The proposed dissolution method and acceptance criteria for the batch release and stability testing of dextromethorphan and bupropion from the FDC tablet are accepted on an interim basis.

PMC 4233

The studies to be performed under this PMC agreement are aimed toward developing an optimal dissolution method for each API to ensure an adequate control of the quality of the proposed ER-FDC 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 for ER-bupropion and IR-dextromethorphan. We recommend developing a clinically relevant dissolution method and acceptance criteria.

-For dextromethorphan, we request that the Applicant use a medium volume (b) (4) as justified by the (b) (4) (b) (4) We also recommend the use of (b) (4) rpm for better discriminating ability.

-For bupropion, we request that the Applicant explore alternate dissolution methods (b) (4) (b) (4) for better discriminating ability.

•To provide the dissolution method development and validation report(s) including detailed justification and complete dissolution data supporting the selection of the dissolution method/testing conditions for each API (e.g., selection of the equipment/apparatus, in vitro dissolution media and media volume, agitation/rotation speed, media pH, sink conditions, use of sinker 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 for each API.

•To provide data supporting the discriminating ability of the selected dissolution method for each API. 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 is able to 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 for each API. Also, to collect complete dissolution profile data for the first six commercial batches of the ER-FDC drug product using the new dissolution methods. Provide all data in Microsoft Excel ".xls or .xlsx" format.

•Based on the overall dissolution data collected using the new dissolution methods, propose the final dissolution acceptance criteria for ER-bupropion and IR-dextromethorphan of the ER-FDC product.

Microbiology (if applicable): Choose an item.

N/A

C. Risk Assessment

From Initial Risk Identification			Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations / Comments**
		H, M, or L		Acceptable or Not Acceptable	
Assay, Stability	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipments • Site	L	Controlled by specification	Acceptable	
Physical stability (solid state) (dextromethorpan is considered BCS II and bupropion is BCS I)	• Formulation • Raw materials • Process parameters • Scale/equipments • Site	L/M	Controlled by specification	Acceptable	
Content uniformity	• Formulation • Raw materials • Process parameters • Scale/equipments • Site	M	Controlled by specification	Acceptable	
Microbial limits	• Formulation • Raw materials • Process parameters • Scale/equipments • Site	L	Controlled by specification	Acceptable	

Dissolution – BCS Class I & III (bupropion is BCS I)	• Formulation • Raw materials • Process parameters • Scale/equipments • Site	L	Controlled by specification	Acceptable (with PMC)	
Dissolution – BCS Class II & IV (dextromethorphan is considered BCS II)	• Formulation • Raw materials • Exclude major reformulations • Process parameters • Scale/equipments • Site	M	Controlled by specification	Acceptable (with PMC)	
Delamination (for multilayered tablets only)	• Formulation • Process parameters • Scale/equipments • Site	L	Controlled by specification	Acceptable	
Alcohol dose dumping	• Formulation • Process parameters • Scale/equipments • Site	H	See original review and information added to labeling	Acceptable	

D. List of Deficiencies for Complete Response

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

2. Drug Substance Deficiencies

3. Drug Product Deficiencies

4. Labeling Deficiencies

5. Manufacturing Deficiencies

6. Biopharmaceutics Deficiencies

7. Microbiology Deficiencies

8. Other Deficiencies (Specify discipline, such as Environmental)

QUALITY ASSESSMENT DATA SHEET

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Comments
(b) (4)	II		(b) (4)	1	13 Apr 20	Reviewed by Siba Bhattacharyya
	II			1	21 Jan 21	Reviewed by Steven Kinsley
	III			4		
	III			4		
	III			4		

Action codes for DMF Table:
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2 –Type 1 DMF
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4 – Sufficient information in application
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6 – DMF not available
7 – Other (explain under "Comments")

B. OTHER DOCUMENTS: *IND, RLD, RS, Approved NDA*

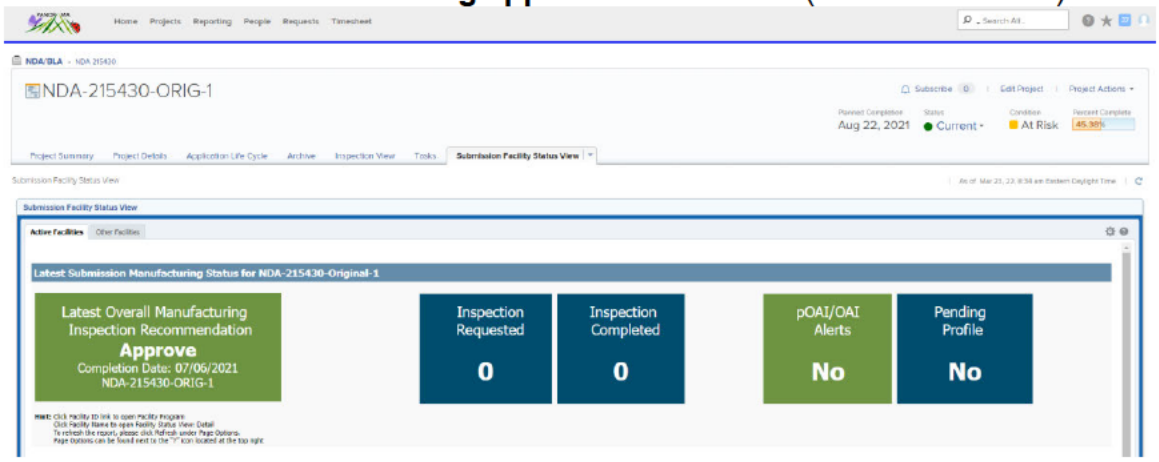
Document	Application Number	Description
IND	124813	
NDA	021879	Nuedexta (dextromethorphan

		hydrobromide / quinidine sulfate) capsules
NDA	020358	Wellbutrin SR (bupropion hydrochloride) sustained-release tablets

2. CONSULTS

Discipline	Status	Recommendation	Date	Assessor
Biostatistics				
Pharmacology/Toxicology				
CDRH-ODE				
CDRH-OC				
Clinical				
Other				

Panorama screenshot showing approval of facilities (taken 23 Mar 22)



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U.S. FOOD & DRUG ADMINISTRATION

CHAPTER VI: BIOPHARMACEUTICS

IQA NDA Assessment Guide Reference

NDA Number	NDA-215430-ORIG-1
Assessment Cycle Number	1
Drug Product Name/ Strength	AXS-05 (Dextromethorphan HBr and Bupropion HCl) Extended-Release Tablets/45 mg and 105 mg
Route of Administration	Oral
Applicant Name	Axsome Therapeutics, Inc.
Therapeutic Classification/ OND Division	Division of Psychiatry (DP)
RLD/RS Number	Reference Drugs Nuedexta® (Dextromethorphan hydrobromide/ Quinidine sulfate Capsules, NDA 021879) and Wellbutrin SR® (Bupropion hydrochloride Sustained-Release Tablets, NDA 020358)
Proposed Indication	Major Depressive Disorder (MDD)
Primary Reviewer	Kalpana Paudel, Ph.D.
Secondary Reviewer	Ta-Chen Wu, Ph.D.

Assessment Recommendation: **Adequate**

Assessment Summary:

Axsome Therapeutics, Inc. (Axsome) submitted NDA 215430 for AXS-05 tablets which is an extended-release fixed-dose combination (FDC) product (i.e., extended-release (ER) bupropion HCl and immediate-release (IR) dextromethorphan HBr). The extended-release designation claim, in vitro alcohol-induced dose-dumping potential, and formulation bridging for the proposed drug product were found to be acceptable in the Biopharmaceutics review dated 07/08/2021 in Panorama. However, the Applicant's proposed single dissolution method for dextromethorphan HBr and bupropion HCl was not acceptable. The Applicant was advised to develop separate dissolution methods with demonstrated discriminating ability for each API of the proposed drug product and submit the data by December 2021. In response to an Information Request (IR) conveyed on 11/10/2021 (See ***Appendix 1***), the Applicant submitted two separate dissolution methods for each component of the proposed drug product in an amendment dated 12/29/2021. This review is focused on evaluation and acceptability of the proposed dissolution methods and acceptance criteria for dextromethorphan HBr and bupropion HCl with key findings summarized below.

Dissolution Method and Acceptance Criteria – Accepted on an interim basis

The submitted dissolution methods are not considered suitable because the selected dissolution method conditions are not adequately justified (including using 900 mL (b) (4) as dissolution volume) and limited discriminating ability was demonstrated towards changes in critical quality attributes. These deficiencies could not

be addressed during the review cycle. Therefore, the currently proposed dissolution method and acceptance criteria for immediate-release dextromethorphan HBr and the extended-release bupropion HCl are accepted only on an interim basis, whereas the Applicant will be requested to develop an optimized dissolution method for each component (dextromethorphan HBr and bupropion HCl) of the FDC product. The Applicant should investigate various dissolution test conditions/parameters, collect dissolution profile data using the new method, and propose as part of the Post-Marketing Commitment (PMC), the final dissolution acceptance criteria for the immediate-release dextromethorphan HBr and extended-release bupropion HCl components of the FDC product.

The Applicant agreed to the PMC on 03/18/2022 via email and will submit the interim and final PMC reports within 9 months and 12 months, respectively, from the NDA's action date. Refer to ***Appendix 2*** for the PMC # 4233.

The following dissolution method and acceptance criteria for batch release and stability testing of dextromethorphan and bupropion from the FDC tablet are accepted on an **interim** basis:

Component	USP Apparatus	Speed (RPMs)	Medium/ Temperature	Volume (mL)	Acceptance criteria
Dextromethorphan	I (Basket)	75	0.1N HCl/ 37°C ± 0.5°C	900	NLT (b) (4)% (Q= (b) (4)%) at 30 minutes
Bupropion	I (Basket)	75	0.01N HCl/ 37°C ± 0.5°C	900	0.5 hr: (b) (4)% 2 hr: (b) (4)% 4 hr: (b) (4)% 8 hr: NLT (b) (4)%

Recommendation:

From the Biopharmaceutics perspective, NDA 215430 for the proposed AXS-05 (dextromethorphan 45 mg and bupropion 105 mg) Extended-Release Tablets is recommended for approval. The proposed dissolution method and acceptance criteria for the batch release and stability testing of dextromethorphan and bupropion from the FDC tablet are accepted on an interim basis

List Submissions being assessed (table):

Document(s) Assessed	Date Received
Sequence 0026-Response To Information Request	12/29/2021

Highlight Key Issues from Last Cycle and Their Resolution:

None. This is the first review cycle.

Concise Description of Outstanding Issues:
The Applicant is requested to develop optimized dissolution method for each API of the proposed FDC drug product under PMC # 4233.

B.3 DISSOLUTION METHOD AND ACCEPTANCE CRITERIA

Assessment: *Adequate on an interim basis*

Dissolution Method

The Applicant developed separate dissolution method for each API in supporting the current application, i.e., extended-release bupropion HCl and immediate-release dextromethorphan HBr of the proposed FDC extended-release drug product. The proposed dissolution method conditions are provided below:

Table 1: Dissolution Method for Dextromethorphan and Bupropion in AXS-05 FDC Tablet

Component	USP Apparatus	Speed (RPMs)	Medium/ Temperature	Volume (mL)	Acceptance criteria
Dextromethorphan	I (Basket)	75	0.1N HCl/ 37°C ± 0.5°C	900	NLT (b) (4)% (Q (b) (4)%) at 30 minutes
Bupropion	I (Basket)	75	0.01N HCl/ 37°C ± 0.5°C	900	0.5 hr: (b) (4)% 2 hr: (b) (4)% 4 hr: (b) (4)% 8 hr: NLT (b) (4)%

Dissolution method development

Dextromethorphan

(b) (4)

[redacted]

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(b) (4)

Discriminating ability of the dissolution method

The Applicant provided data for discriminating ability of the dissolution method for variations in the formulation and process parameters using above selected method and are summarized below.

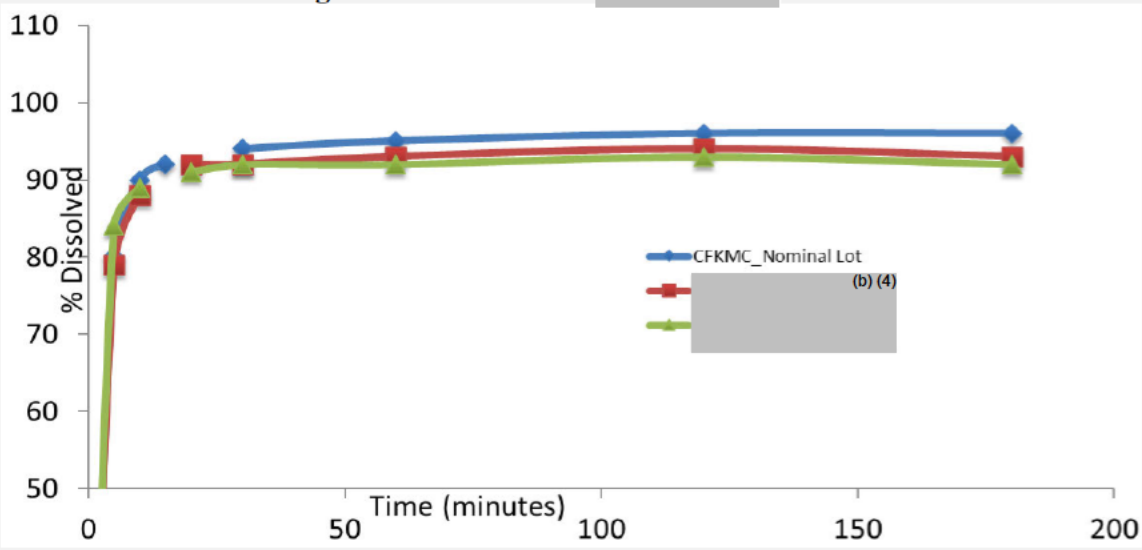
Table 4: Formulation of AXS-05 Bilayer Tablets

(b) (4)

Evaluation of (b) (4) Ratio in the Formulation

(b) (4) is (b) (4) used in the (b) (4) AXS-05 tablets. The (b) (4) quantities were varied from the nominal lot (b) (4) to (b) (4) (b) (4) in the experimental formulations and compared against the dissolution of the nominal lot. No discrimination was observed between the variable quantities of (b) (4) in the formulation as seen in the figure below.

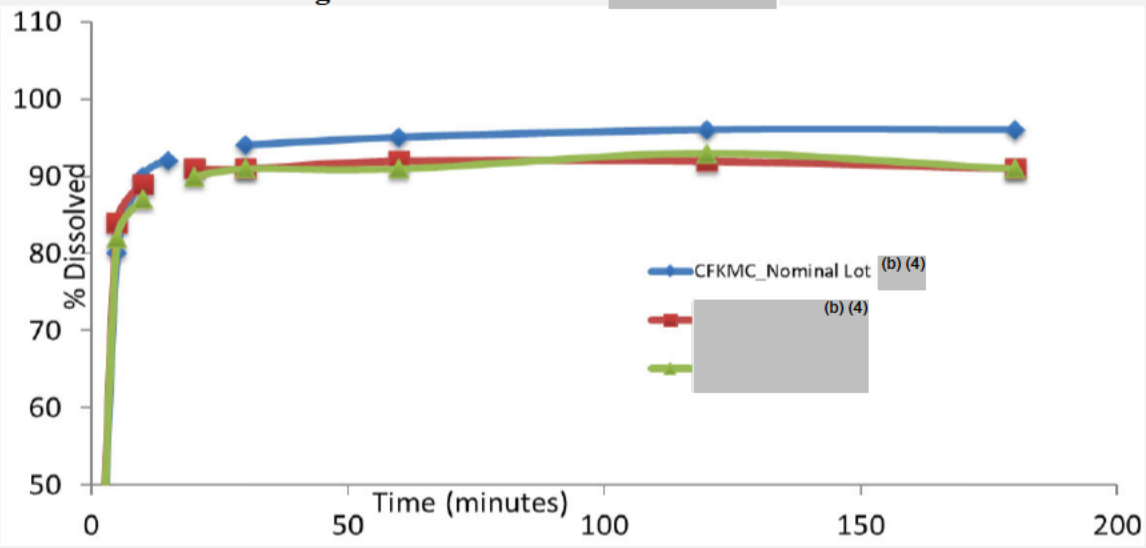
Figure 6: Evaluation of (b) (4) Ratio



Evaluation of (b) (4) Ratio in the Formulation

(b) (4) quantities were varied from the nominal lot (b) (4) to (b) (4) (b) (4) in the experimental formulations and compared against the dissolution of the nominal lot. No significant change in the dissolution release was observed with the variable quantities of (b) (4) in the formulation as seen in the figure below.

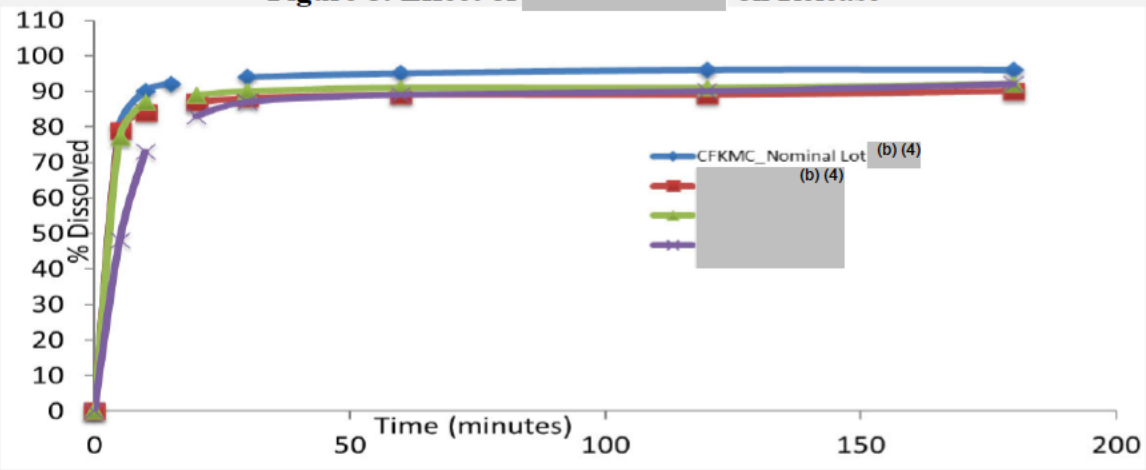
Figure 7: Evaluation of (b) (4) Ratio



Variation in (b) (4) trials

The nominal (b) (4) amount of AXS-05 product is (b) (4) of (b) (4) (b) (4), representing a (b) (4). Formulations were made with (b) (4). Only the formulation with (b) (4) showed some (b) (4) Tablets with all other variations (b) (4) had no observed impact on the dissolution release rate as shown in the figure below.

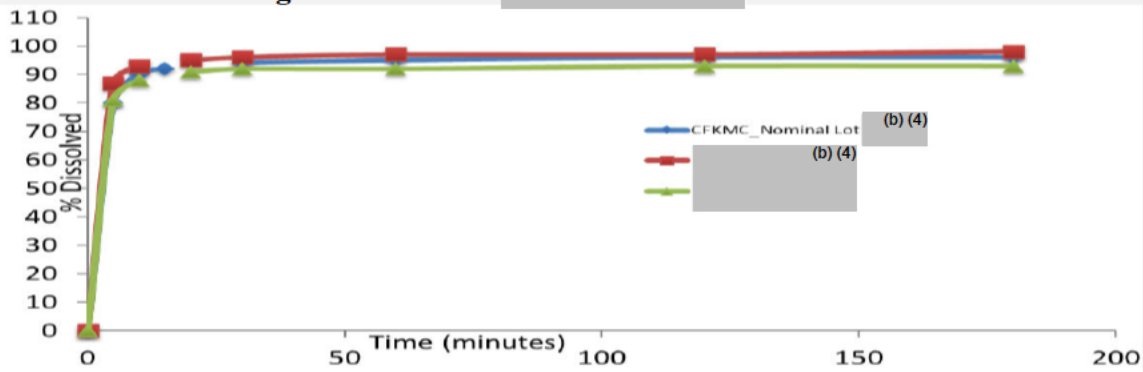
Figure 8: Effect of (b) (4) on Release



Variation in (b) (4)

The nominal [redacted] of AXS-05 product is [redacted]. Various formulations were made with [redacted] and [redacted]. [redacted] had minimal impact on the release of the dextromethorphan as summarized in the figure below.

Figure 9: Effect of [redacted] on Release



Bupropion

Report of the dissolution method development for the release of bupropion is provided in the link below:
\\CDSESUB1\evsprod\nda215430\0026\m1\us\1-11-1-att-bupropion-diss-synopsis.pdf
A summary of the justification for the selection of dissolution method parameters is provided below.

[redacted]

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(b) (4)

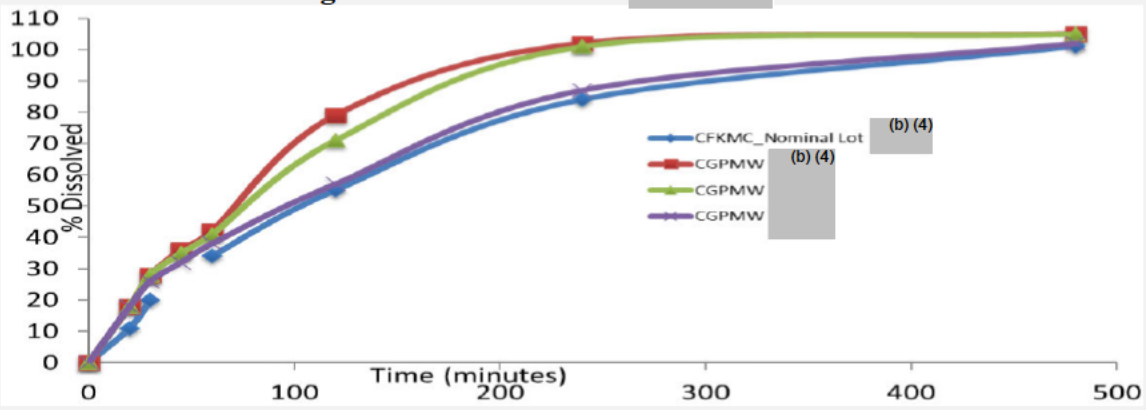
Discriminating ability of the dissolution method

The Applicant provided data for discriminating ability of the dissolution method for variations in the formulation and process parameters using above selected method which are summarized below.

Evaluation of (b) (4) Ratio in the Formulation

(b) (4) is the (b) (4) for bupropion in AXS-05. The (b) (4) quantities were varied from the nominal lot (b) (4) (b) (4) to (b) (4) in the experimental formulations and compared against the dissolution of the nominal lot. A notable discrimination was observed (figure below) between the variable quantities of (b) (4) in the formulation compared to the nominal lot based on the similarity value (f2) as calculated by this reviewer (37, 44.9, and 49.4 for three strengths).

Figure 15: Evaluation of (b) (4) Ratio

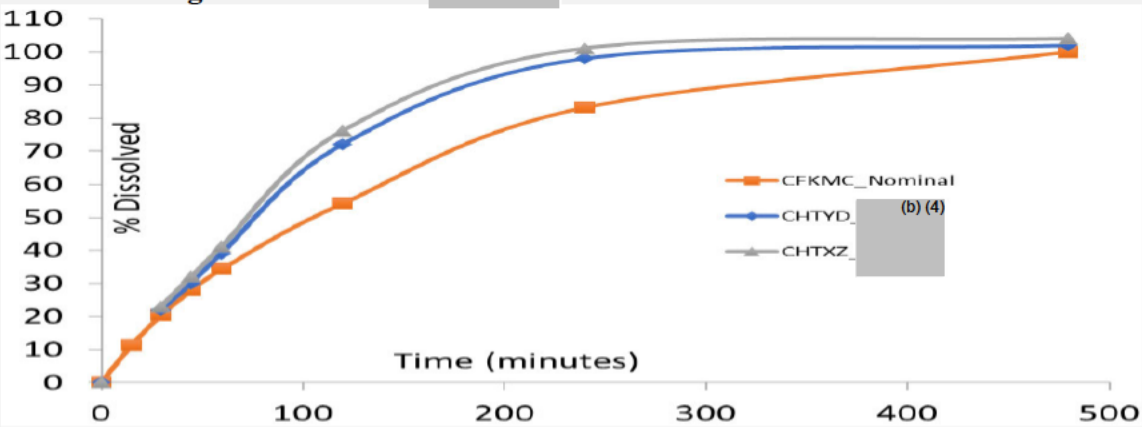


Assessment of (b) (4) Material Attributes for Drug Release

The (b) (4) and the (b) (4) content of (b) (4) were evaluated for their impact on bupropion dissolution. (b) (4) around (b) (4) and (b) (4) content of

greater than [redacted] showed [redacted] release of the drug (figure below) compared to AXS-05 tablets formulated with [redacted] and were different based on the similarity value (f2) as calculated by this reviewer (48.3 and 43.8 for batches CHTYD and CHTXZ, respectively).

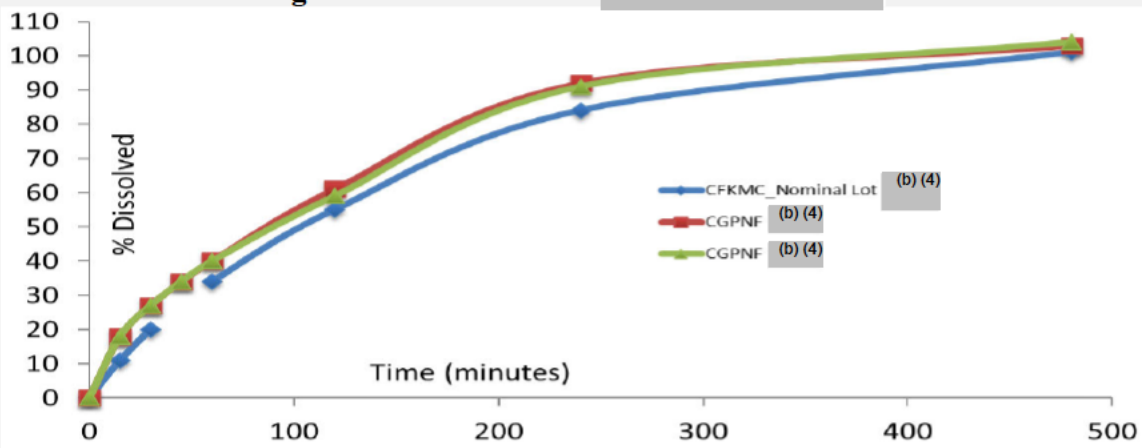
Figure 16: Effect of [redacted] Material Attributes on Release



Evaluation of [redacted] Ratio in the Formulation

[redacted] quantities were varied from the nominal lot [redacted] to [redacted] in the formulation and compared against the dissolution of the nominal lot (figure below). No change in dissolution was observed with the variable quantities of [redacted] in the formulation.

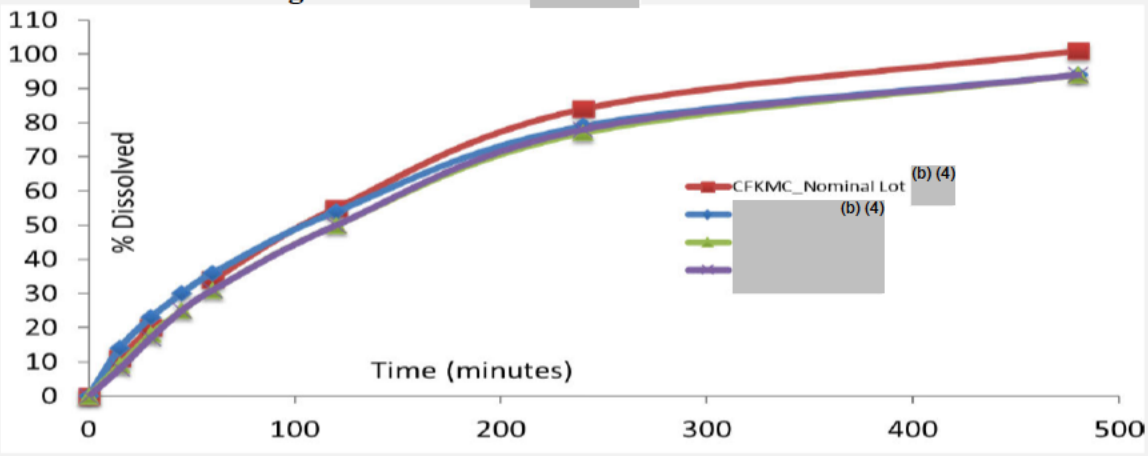
Figure 17: Evaluation of [redacted]



Variation in [redacted] Trails

The nominal [redacted] amount of AXS-05 product is [redacted] of [redacted], representing a [redacted]. Formulations were made with [redacted]. No change in dissolution was observed with variable [redacted] (figure below).

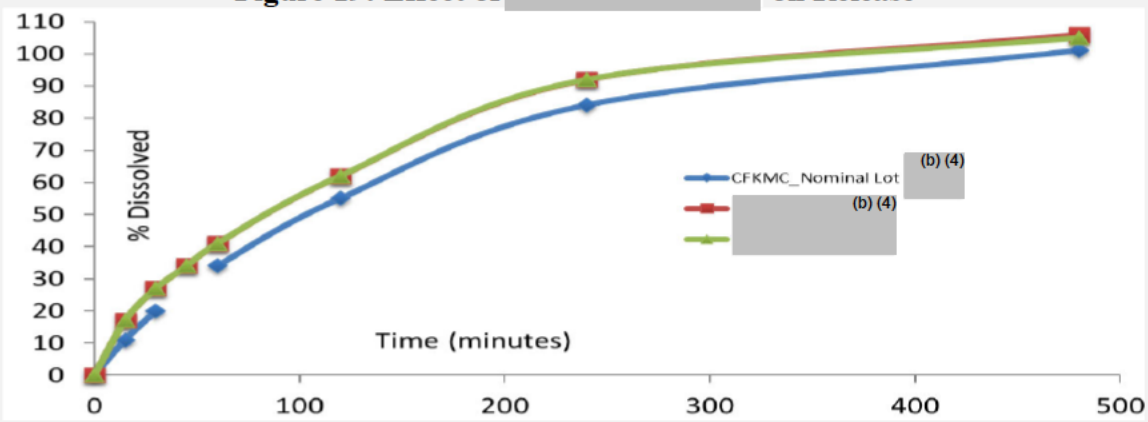
Figure 18: Effect of (b) (4) Levels on Release



Variation in (b) (4)

The nominal (b) (4) of AXS-05 product is (b) (4). Various formulations were made with (b) (4) and (b) (4). No change in dissolution was observed (figure below).

Figure 19: Effect of (b) (4) on Release



Reviewer's Comments:

For **dextromethorphan**, the Applicant proposed Apparatus I at 75 rpm and 900 mL of 0.1N HCl as the dissolution method conditions. The Applicant stated that a media volume of 900 mL was chosen (b) (4) (b) (4) (b) (4) In addition, the proposed dissolution method could not discriminate the critical quality attributes within the ranges tested. Therefore, the Applicant will be requested to use (b) (4) (b) (4) as dissolution medium for dextromethorphan in view of (b) (4)

(b) (4) and to use (b) (4) rpm for better discriminating ability of the method.

For **bupropion**, the Applicant proposed Apparatus I at 75 rpm and 900 mL of 0.01N HCl media as the dissolution method conditions. However, (b) (4) (b) (4). In addition, the proposed dissolution method exhibited limited discriminating ability towards changes in critical quality attributes. Hence, the Applicant will be requested to explore alternate dissolution methods (b) (4) for better discriminating ability.

The above issues could not be addressed during the review cycle because of short review timeline for this NDA. Therefore, the currently proposed dissolution method and acceptance criteria for immediate-release dextromethorphan HBr and the extended-release bupropion HCl are accepted only on an interim basis, whereas the Applicant will be requested to develop an optimized dissolution method for each component (dextromethorphan HBr and bupropion HCl) of the FDC product. The Applicant should investigate various dissolution test conditions/parameters, collect dissolution profile data using the new method, and propose as part of the PMC, the final dissolution acceptance criteria for the immediate-release dextromethorphan HBr and extended-release bupropion HCl components of the FDC product (See ***Appendix 2*** for PMC details).

Dissolution Acceptance Criteria

The Applicant evaluated four lots of currently available unexpired drug product using the new separate dissolution methods. The Applicant noted that they proposed preliminary acceptance criteria for the new separate dissolution methods that are the same as those for the current combined method because the dissolution results obtained from these analyses are consistent with the current acceptance criteria ranges proposed for both bupropion and dextromethorphan dissolution (as agreed in SN0019).

The lots evaluated were CHGFW (Clinical trial material, CTM), CFKMC (registration-scale demonstration), and CFTDV and CFTDW (registration). A summary of the dissolution results of these batches are provided in the tables and figure below.

Table 7: Bupropion Dissolution Data for AXS-05 Drug Product Using the New Method Compared to Current Acceptance Criteria

Timepoint	CHFGW	CFKMC	CFTDV	CFTDW	NDA Acceptance Criteria for Combined Dissolution Method
0.5 hours	Min – Max (b) (4)% **Avg 22%**	Min – Max (b) (4)% **Avg 21%**	Min – Max (b) (4)% **Avg 23%**	Min – Max (b) (4)% **Avg 21%**	(b) (4)%
2 hours	Min – Max (b) (4)% **Avg 56%**	Min – Max (b) (4)% **Avg 56%**	Min – Max (b) (4)% **Avg 56%**	Min – Max (b) (4)% **Avg 56%**	(b) (4)%
4 hours	Min – Max (b) (4)% **Avg 84%**	Min – Max (b) (4)% **Avg 84%**	Min – Max (b) (4)% **Avg 85%**	Min – Max (b) (4)% **Avg 85%**	(b) (4)%
8 hours	Min – Max (b) (4)% **Avg 100%**	Min – Max (b) (4)% **Avg 100%**	Min – Max (b) (4)% **Avg 100%**	Min – Max (b) (4)% **Avg 101%**	NLT (b) (4)%

NLT = not less than.

Figure 20: Bupropion Dissolution Chart for AXS-05 Drug Product Using New Method Compared to Current Acceptance Criteria

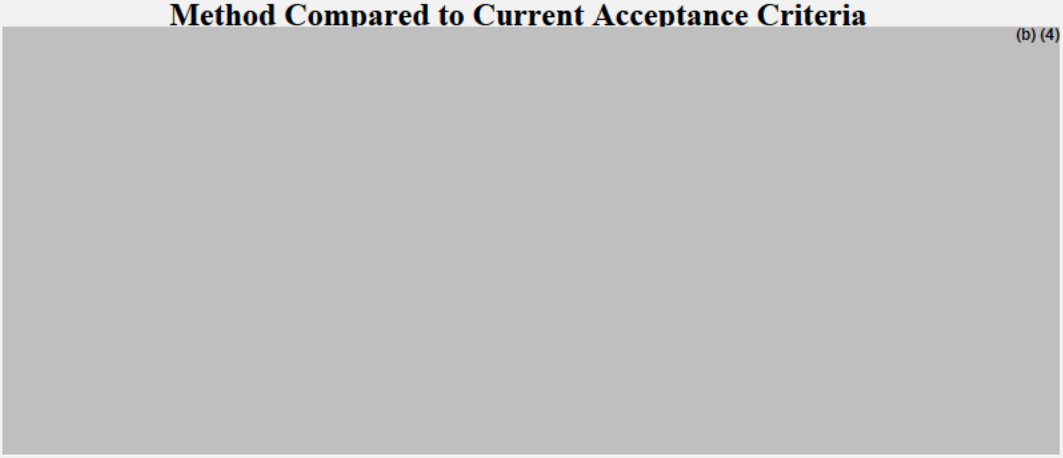


Table 7: Dextromethorphan Dissolution Data for AXS-05 Drug Product Using the New Method Compared to Current Acceptance Criteria

Timepoint	CFKMC	CFTDV	CFTDW	CHFGW	NDA Acceptance Criteria for Combined Dissolution Method
30 minutes	Min – Max (b) (4)% **Avg 93%**	Min – Max (b) (4)% **Avg 94%**	Min – Max (b) (4)% **Avg 95%**	Min – Max (b) (4)% **Avg 93%**	NLT (b) (4)% (Q= (b) (4))

NLT = not less than.

Reviewer's Comments:

The Applicant's proposed dissolution acceptance criteria are accepted on an interim basis. The Applicant will be requested to develop optimized dissolution methods and to propose new sets of dissolution acceptance criteria for each API of the drug product based on the newly generated data (see ***Appendix 2***).

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Kalpana Paudel

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Date: 3/21/2022 05:14:14PM
GUID: 562e1e15002f200f35c6ccac959cdb34

Ta-Chen Wu

Digitally signed by Ta-Chen Wu
Date: 3/21/2022 05:25:15PM
GUID: 508da6df000269e151ff37cd8f4e13a1

Valerie Amspacher

Digitally signed by Valerie Amspacher
Date: 3/23/2022 03:41:27PM
GUID: 5714dbd10078d2d3d9b60a0ceb819fc3

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/

VALERIE R AMSPACHER
03/23/2022 03:55:37 PM

Table of Contents

U.S. FOOD & DRUG ADMINISTRATION

RECOMMENDATION

☐ Approval
☐ Approval with Post-Marketing Commitment
☒ Complete Response

NDA # 215430
Assessment # 1

Drug Product Name	AXS-05 (dextromethorphan-bupropion)
Dosage Form	tablet
Strength	45 mg (dextromethorphan HBr) / 105 mg (bupropion HCl)
Route of Administration	oral
Rx/OTC Dispensed	Rx
Applicant	Axsome Therapeutics, Inc.
US agent, if applicable	N/A

Submission(s) Assessed	Document Date	Discipline(s) Affected
Supporting document 1; eCTD 0001	22 Feb 21	All, original submission
Supporting document 10; eCTD 0010	2 Apr 21	Drug product, process/facilities, biopharmaceutics
Supporting document 15; eCTD 0015	7 Jun 21	Process/facilities
Supporting document 18; eCTD 0018	24 Jun 21	Biopharmaceutics
Supporting document 19; eCTD 0019	30 Jun 21	Biopharmaceutics
Supporting document 21; eCTD 0021	2 Jul 21	Process/facilities

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessment	Secondary Assessment
Drug Substance	Gaetan Ladouceur	Donna Christner
Drug Product	Renish Delvadia	Julia Pinto
Manufacturing	Teng (Daisy) Xu	Sharmista Chatterjee
Microbiology	N/A	N/A
Biopharmaceutics	Kalpana Paudel	Ta-Chen Wu

Regulatory Business Process Manager	Teshara Bouie	
Application Technical Lead	Valerie Amspacher	
Laboratory (OTR)	N/A	N/A
Environmental	Renish Delvadia	Julia Pinto

EXECUTIVE SUMMARY

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

CMC recommends complete response for this NDA based on the drug product and biophamaceutics review. Drug substance and process/facilities reviews recommend approval.

A 6 month shelf-life is acceptable when stored at 25˚C.

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

AXS-05 is an oral, fixed-dose, combination of dextromethorphan hydrobromide (HBr) and bupropion hydrochloride (HCl). AXS-05 is formulated into round, beige film-coated bilayer tablets. The bupropion HCl in the tablets is formulated for extended release, and the dextromethorphan HBr is formulated for immediate release. The commercial drug product will be debossed on one side with “45/105” and will be plain on the other side.

A 6 month shelf-life is acceptable when stored at 25˚C.

Proposed Indication(s) including Intended Patient Population	Treatment of Major Depressive Disorder
Duration of Treatment	chronic
Maximum Daily Dose	Dextromethorphan 90 mg; bupropion 210 mg
Alternative Methods of Administration	N/A

B. Quality Assessment Overview

Drug Substance: Adequate

Bupropion Hydrochloride drug substance is cross-referenced to DMF (b) (4), which was last reviewed by the Agency on 04/13/2020 (adequate), while Dextromethorphan hydrobromide is cross-referenced to DMF (b) (4), which was last reviewed by the Agency on 1/21/2021 (adequate). The retest period for both drug substance is (b) (4) months. A shelf life of 6 months is proposed for the drug product.

Drug Product: Inadequate

The proposed drug product is an oral, fixed-dose, combination of 45 mg dextromethorphan HBr and 105 mg bupropion hydrochloride HCl, formulated into bilayer tablets. The bupropion HCl in the tablets is formulated for extended-release, and the dextromethorphan HBr is formulated for immediate release.

The excipients used in the proposed formulation are of pharmacopeial grade, and typically used in extended-release tablet products. No novel/animal origin excipients used in the proposed formulation.

The Applicant has performed adequate product development studies to justify the selection of the excipients and to demonstrate/justify their chemical compatibility with the drug substance. The tablets are packaged in high-density polyethylene (HDPE) bottles.

The Applicant has provided 6-months of long-term, intermediate, and accelerated stability data for three registration batches, and additional stability data for two smaller batches. No stability trend observed within 6 months during the long-term stability. Declining in dissolution trend was observed for bupropion HCl, which was more pronounced in the accelerated stability samples; all long term stability data were within the most recently proposed specification. Overall, the submitted stability data supports the proposed shelf-life of 6-months.

The limit of quantification (LOQ) for degradants in the drug product is (b) (4)%. It is typically expected that the analytical methods for degradants of the drug product has LOQ of (b) (4)% or below to adequately capture the stability trend of drug product degradants. The Applicant will be asked to revise and/or revalidate the current analytical method to attain the LOQ≤ (b) (4)%.

Labeling: Adequate

Manufacturing: Adequate

Dextromethorphan hydrobromide and bupropion hydrochloride tablets, 45 mg/105 mg is an oral, fixed-dose combination, film-coated bilayer tablets of dextromethorphan hydrobromide (HBr) and bupropion hydrochloride (HCl). The bupropion HCl in the tablets is formulated for extended release, and the dextromethorphan HBr is formulated for immediate release. (b) (4)

(b) (4)

(b) (4)

(b) (4) The manufacturing process included the following key steps: (b) (4)

(b) (4)

The registration batch size is (b) (4) kg with approximately (b) (4) tablets and the proposed commercial batch size will be (b) (4) kg with approximately (b) (4) (Overall, (b) (4) scale-up). Two sublots of (b) (4) are included in the registration batch process, whereas six sublots will be included in the commercial process. (b) (4)

(b) (4)

Following the review of the application and inspection documents, there were no significant outstanding manufacturing or facility risks that prevent approval of this application. The manufacturing facilities for NDA 215430 were found acceptable.

Biopharmaceutics: Inadequate

The AXS-05 extended-release (ER) tablet is a fixed-dose combination (FDC) tablet containing 45 mg dextromethorphan HBr (DM) in an immediate-release (IR) formulation and 105 mg bupropion HCl in a sustained-release formulation for twice daily administration.
The Applicant developed a single dissolution method for both APIs of the proposed FDC product (i.e., bupropion HCl (ER) and dextromethorphan HBr (IR)). The proposed single dissolution method is not appropriate for a combination product including both ER and IR components. The discriminating ability of the method towards changes in the critical quality attributes of both APIs is very limited.
During the review cycle, the Applicant was advised to develop separate dissolution methods with adequate discriminating ability for each component. However, the Applicant was not able to address this request because of the review timeline for this priority NDA submission.
Therefore, it was determined that the proposed single dissolution method is inadequate. The Applicant will be requested to develop and validate optimal dissolution methods for each component of AXS-05 ER Tablets, FDC product (i.e., extended-release bupropion HCl and immediate-release dextromethorphan HBr) and propose dissolution acceptance criteria proposal drug product based on the newly generated data.

Extended release claim

The proposed ER drug product was shown to have comparable steady-state performance of the bupropion component of AXS-05 to the currently marketed bupropion sustained release drug product (Zyban) following once daily dose for 8 days. Pharmacokinetic data from eleven studies with AXS-05 rule out the occurrence of dose-dumping, with consistent delivery of bupropion into the systemic circulation with coefficients of variations for Cmax and AUC of approximately 25% on Day 1 and at steady-state. These data support the extended release claim and were deemed acceptable, per the 21 CFR 320.25(f).

In Vitro Alcohol-Induced Dose-Dumping
For bupropion, no dose dumping was observed for up to 8 hours in the presence of various alcohol concentrations up to 40% (v/v); instead, there were alcohol concentration dependent but insignificant decreases in drug release/dissolution of bupropion. Various alcohol concentrations up to 40% (v/v) did not affect the drug release of dextromethorphan up to 8 hours.

Formulation Bridging
Comparative in vitro dissolution studies were conducted to bridge tablet formulation (Version (b) (4) used in Pivotal Phase 3 clinical studies and the commercial tablets (Version (b) (4)) used in food effect and Phase 3 study, differing in composition. Dissolution testing in 0.1 N HCl, 0.1 M Acetate buffer at pH 4.5, and 0.1 M Phosphate buffer at pH 6.8 showed similarity in drug release between Version (b) (4) and Version (b) (4) tablets, as demonstrated by f2 value greater than 50 for bupropion HCl and greater than (b) (4) % percent dissolution in 30 minutes for dextromethorphan HBr. Batch release data also showed similarity between Version (b) (4) and Version (b) (4) tablets for both components. In vivo comparability of Version (b) (4) and Version (b) (4) tablets was also demonstrated by similar drug exposures of bupropion and dextromethorphan across Phase 1 pharmacokinetic (PK) studies. These in vivo studies are under the purview of the OCP review team.

Microbiology (if applicable): Choose an item.

N/A

C. Risk Assessment

From Initial Risk Identification			Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations / Comments**

		H, M, or L		Acceptable or Not Acceptable	
Assay, Stability	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipments • Site	L	Controlled by specification	Not Acceptable	
Physical stability (solid state) (dextromethorpan is considered BCS II and bupropion is BCS I)	• Formulation • Raw materials • Process parameters • Scale/equipments • Site	L/M	Controlled by specification	Acceptable	
Content uniformity	• Formulation • Raw materials • Process parameters • Scale/equipments • Site	M	Controlled by specification	Acceptable	
Microbial limits	• Formulation • Raw materials • Process parameters • Scale/equipments • Site	L	Controlled by specification	Acceptable	
Dissolution – BCS Class I & III (bupropion is BCS I)	• Formulation • Raw materials • Process parameters • Scale/equipments • Site	L	Controlled by specification	Not Acceptable	
Dissolution – BCS Class II & IV (dextromethorphan is considered BCS II)	• Formulation • Raw materials • Exclude major reformulations • Process parameters • Scale/equipments • Site	M	Controlled by specification	Not Acceptable	

Delamination (for multilayered tablets only)	• Formulation • Process parameters • Scale/equipments • Site	L	Controlled by specification		
Alcohol dose dumping	• Formulation • Process parameters • Scale/equipments • Site	H	See original review and information added to labeling	Acceptable	

D. List of Deficiencies for Complete Response

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

2. Drug Substance Deficiencies

3. Drug Product Deficiencies

Deficiency:
We note that the proposed analytical methods for quantification of related substances in the drug product has limit of quantification (LOQ) of (b) (4)%. We are concerned that these analytical methods might not be adequately sensitive to capture the stability trend of the impurities/degradants in the drug product.

Information needed to resolve deficiency:
To further improve overall analytical method sensitivity, revise and/or validate the current analytical methods with LOQ of (b) (4)% or below.

4. Labeling Deficiencies

5. Manufacturing Deficiencies

6. Biopharmaceutics Deficiencies

Deficiency:
The NDA provides a single dissolution method for both bupropion and dextromethorphan components of the proposed drug product, which is deemed not optimal for each API.

Information needed to resolve deficiency:

Develop and validate an optimal dissolution method for each component of AXS-05 ER Tablets, FDC product (i.e., extended-release bupropion HCl and immediate-release dextromethorphan HBr). Submit final dissolution acceptance criteria proposal for AXS-05 ER Tablets, based on the data generated from the unexpired clinical and registration batches, and the first six commercial batches, using the new dissolution method. SPQA note – the wording of this deficiency has changed slightly from the biopharm review however the content/intent remains identical to that of the biopharm review.

7. Microbiology Deficiencies

8. Other Deficiencies (Specify discipline, such as Environmental)

QUALITY ASSESSMENT DATA SHEET

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Comments
(b) (4)	II		(b) (4)	1	13 Apr 20	Reviewed by Siba Bhattacharyya
	II			1	21 Jan 21	Reviewed by Steven Kinsley
	III			4		
	III			4		
	III			4		

Action codes for DMF Table:
1 – DMF Reviewed.
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review

4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

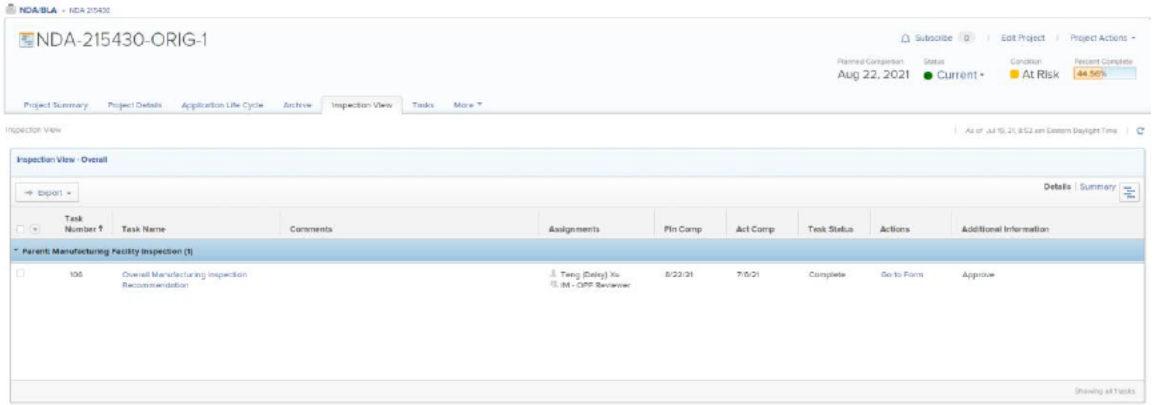
B. OTHER DOCUMENTS: *IND, RLD, RS, Approved NDA*

Document	Application Number	Description
IND	124813	
NDA	021879	Nuedexta (dextromethorphan hydrobromide / quinidine sulfate) capsules
NDA	020358	Wellbutrin SR (bupropion hydrochloride) sustained-release tablets

2. CONSULTS

Discipline	Status	Recommendation	Date	Assessor
Biostatistics				
Pharmacology/Toxicology				
CDRH-ODE				
CDRH-OC				
Clinical				
Other				

Panorama screenshot showing approval of facilities (taken 19 Jul 21)



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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: Due to CR recommendation by the Clinical division, final labeling assessment is pending. CMC assessor's comments for the PI label has been conveyed to the labeling reviewer. Proposed label for container/closure is adequate. The order of API in the established name is currently under review by the clinical division.

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]	Inadequate	Change to (dextromethorphan hydrobromide and bupropion hydrochloride) extended-release tablets The order of API is currently under review by the clinical division.
Route(s) of administration	Adequate	
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system	Inadequate	Extended-release tablets: (b) (4)
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).	Adequate	

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, instructions for mixing with food)	Adequate	
For parenteral products: include statement: *"Parenteral drug products must be inspected visually for particulate matter and*	N/A	

discoloration prior to administration, whenever solution and container permit"		
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).	Adequate	Since both APIs are listed as salt in previously approved products for strength, exception is applicable here.
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

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		Some formatting changes will be conveyed directly through the working label edits.
Proprietary and established name(s)	Inadequate	Not yet finalized; established name not listed in this section.
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)"	Inadequate	Strength listed as amount of salt for each API; USP salt policy exception applies due to previously approved product strength listed as salt. No equivalency statement included in the proposed label.
List names of all inactive ingredients. Use USP/NF names in alphabetical order. Avoid brand names.	Inadequate	List of excipients in (b) (4) not included.
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	Inadequate	Pharmacological class not included
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)	N/A	

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."	Adequate	

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	N/A	Not claimed in the label.

1.2.5 Other Sections of Labeling

None

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	Inadequate	

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]	Inadequate	Change to (dextromethorphan hydrobromide and bupropion hydrochloride) extended-release tablets
Special preparation instructions (if applicable)	N/A	
Storage and handling information (if applicable)	Adequate	
If the product contains a desiccant, ensure the desiccant has a warning (e.g., "Do not eat.") and the size and shape of the desiccant differs from the dosage form.	Adequate	
Active ingredient(s) (if applicable)	Inadequate	
Alphabetical listing of inactive ingredients (if applicable)	Adequate	
Name and location of business (street address, city, state, and zip code) of manufacturer, distributor, and/or packer	Adequate	

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

3.0 CONTAINER AND CARTON LABELING

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

3.1 Container Labels (Submitted in the IR response dated 07/06/2021 via email to RPM, Parihar Simran)

(b) (4)

3.2 Carton Labeling

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

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.	Adequate	
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	
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.	Adequate	
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***

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

ITEMS FOR ADDITIONAL ASSESSMENT

None

Overall Assessment and Recommendation:

Conainer label is adequate

Primary Labeling Assessor Name and Date:Renishkumar Delvadia, 07/15/2021

Secondary Assessor Name and Date (and Secondary Summary, as needed): Julia Pinto, 07/15/2021

Renishkumar Delvadia

Digitally signed by Renishkumar Delvadia
Date: 7/15/2021 11:09:00AM
GUID: 5388ee7d000671ff7781f1835a3ff7b9

Julia Pinto

Digitally signed by Julia Pinto
Date: 7/15/2021 01:08:03PM
GUID: 5050dbcb00001294a888a4bdc20a3a58

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U.S. FOOD & DRUG ADMINISTRATION

CHAPTER VI: BIOPHARMACEUTICS

IQA NDA Assessment Guide Reference

NDA Number	NDA-215430-ORIG-1
Assessment Cycle Number	1
Drug Product Name/ Strength	AXS-05 (Dextromethorphan HBr and Bupropion HCl) Extended-Release Tablets/45 mg and 105 mg
Route of Administration	Oral
Applicant Name	Axsome Therapeutics, Inc.
Therapeutic Classification/ OND Division	Division of Psychiatry (DP)
RLD/RS Number	Reference Drugs Nuedexta® (Dextromethorphan hydrobromide/ Quinidine sulfate Capsules, NDA 021879) and Wellbutrin SR® (Bupropion hydrochloride Sustained-Release Tablets, NDA 020358)
Proposed Indication	Major Depressive Disorder (MDD)
Primary Reviewer	Kalpana Paudel, Ph.D.
Secondary Reviewer	Ta-Chen Wu, Ph.D.

Assessment Recommendation: **Inadequate**

Background:

The Applicant submitted NDA 215430 for the proposed AXS-05 (dextromethorphan HBr and bupropion HCl) Extended-Release tablets which is a combination therapy for the treatment of Major Depressive Disorder (MDD) in adults. The AXS-05 extended-release (ER) tablet is a fixed-dose combination (FDC) tablet containing 45 mg dextromethorphan HBr (DM) in an immediate-release (IR) formulation and 105 mg bupropion HCl in a sustained-release formulation for twice daily administration. bupropion HCl (BUP). AXS-05 was granted Breakthrough Therapy Designation on March 25, 2019. The Applicant is seeking approval under the 505(b)(2) pathway using Reference Drugs, Nuedexta® (Dextromethorphan hydrobromide/ Quinidine sulfate Capsules, NDA 021879, Avanir Pharmaceuticals, Inc) and Wellbutrin SR® (Bupropion hydrochloride Sustained-Release Tablets, NDA 020358, GlaxoSmithKline) to support labeling. The Applicant requested Priority Review Designation for this NDA based on the serious nature of MDD and the demonstrated potential of AXS-05 to provide a significant improvement in effectiveness and safety in the treatment of MDD in adults.

AXS-05 is a novel, oral, N-methyl-D-aspartate (NMDA) receptor antagonist with multimodal activity. The dextromethorphan component of AXS-05 is an uncompetitive NMDA receptor antagonist and a sigma-1 receptor agonist. The bupropion component of AXS-05 serves to increase the plasma concentration of dextromethorphan by inhibiting CYP2D6, thereby enhancing the pharmacological effects of dextromethorphan.

Assessment Summary:

This review is focused on evaluation and acceptability of the proposed dissolution method and acceptance criteria for dextromethorphan HBr and bupropion HCl, extended-release designation claim, in vitro alcohol-induced dose-dumping potential, and formulation bridging, with key findings summarized below.

Dissolution Method and Acceptance Criteria - Inadequate

The Applicant proposed the following dissolution method for the proposed FDA tablet and two sets of acceptance criteria for the releases of dextromethorphan and bupropion from the FDC tablet as quality control (QC) for batch release and stability testing:

(b) (4)

The Applicant developed a single dissolution method for both APIs of the proposed FDC product (i.e., bupropion HCl (ER) and dextromethorphan HBr (IR)). The proposed single dissolution method is not appropriate for a combination product including both ER and IR components. The discriminating ability of the method towards changes in the critical quality attributes of both APIs is very limited.

During the review cycle, the Applicant was advised to develop separate dissolution methods with adequate discriminating ability for each component (***Appendix 1***). However, the Applicant was not able to address this request because of the review timeline for this priority NDA submission. Therefore, it was determined that the proposed single dissolution method is inadequate. The Applicant will be requested to develop and validate optimal dissolution methods for each component of AXS-05 ER Tablets, FDC product (i.e., extended-release bupropion HCl and immediate-release dextromethorphan HBr) and propose dissolution acceptance criteria proposal drug product based on the newly generated data (***Appendix 2***).

Extended Release Claim: Adequate

The proposed ER drug product was shown to have comparable steady-state performance of the bupropion component of AXS-05 to the currently marketed bupropion sustained release drug product (Zyban) following once daily dose for 8 days. Pharmacokinetic data

from eleven studies with AXS-05 rule out the occurrence of dose-dumping, with consistent delivery of bupropion into the systemic circulation with coefficients of variations for Cmax and AUC of approximately 25% on Day 1 and at steady-state. These data support the extended release claim and were deemed acceptable, per the 21 CFR 320.25(f).

In Vitro Alcohol-Induced Dose-Dumping: Adequate
The in vitro alcohol-induced dose dumping potential was investigated in 0.1 N HCl in the presence of various concentrations of alcohol (0%, 5%, 10%, 20%, and 40%). For bupropion, no dose dumping was observed for up to 8 hours in the presence of various alcohol concentrations up to 40% (v/v); instead, there were alcohol concentration-dependent but insignificant decreases in drug release/dissolution of bupropion. Various alcohol concentrations up to 40% (v/v) did not affect the drug release of dextromethorphan up to 8 hours.

Formulation Bridging: Adequate
Initial formulation (Version (b) (4) shares the same composition as Version (b) (4) (tablet formulation used in Pivotal Phase 3 clinical studies), thus no bridging is necessary. Comparative in vitro dissolution studies were conducted to bridge tablet formulation (Version (b) (4) used in Pivotal Phase 3 clinical studies and the commercial tablets (Version (b) (4)) used in food effect and Phase 3 study, differing in composition. Dissolution testing in 0.1 N HCl, 0.1 M Acetate buffer at pH 4.5, and 0.1 M Phosphate buffer at pH 6.8 showed similarity in drug release between Version (b) (4) and Version (b) (4) tablets, as demonstrated by f2 value greater than 50 for bupropion HCl and greater than (b) (4) % percent dissolution in 30 minutes for dextromethorphan HBr. Batch release data also showed similarity between Version (b) (4) and Version (b) (4) tablets for both components. *In vivo* comparability of Version (b) (4) and Version (b) (4) tablets was also demonstrated by similar drug exposures of bupropion and dextromethorphan across Phase 1 pharmacokinetic (PK) studies. These in vivo studies are under the purview of the OCP review team.

Recommendation:
From the Biopharmaceutics perspective, NDA 215430 for the proposed AXS-05 (dextromethorphan 45 mg and bupropion 105 mg) Extended Release Tablets is **inadequate** for approval. Biopharmaceutics Deficiency as listed in Appendix 2 will be conveyed to the Applicant.

List Submissions being assessed (table):

Document(s) Assessed	Date Received
Sequence 0001-Original submission	02/22/2021
Sequence 0010-Response To Information Request	04/02/2021
Sequence 0015-Response To Information Request	06/07/2021
Sequence 0018-Response To Information Request	06/24/2021
Sequence 0019-Response To Information Request	06/30/2021

Highlight Key Issues from Last Cycle and Their Resolution:
None. This is the first review cycle.

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 each API of the proposed FDC drug product.

B.1 BCS DESIGNATION

Assessment:
Based on the submitted data by the Applicant, Dextromethorphan HBr has low aqueous solubility. Bupropion HCl exhibits good solubility and is classified as BCS Class I. However, no permeability data are provided for the APIs.

Solubility:
Bupropion HCl
Bupropion HCl exhibits good solubility in water and is classified as BCS Class I.

Dextromethorphan HBr
Dextromethorphan HBr is sparingly soluble across the pH range of 1.2 to 7.5. Aqueous solubility of dextromethorphan HBr is provided in Table 1.

Table 1: Aqueous Solubility of Dextromethorphan HBr as a Function of pH

pH	Solubility
1.2 pH buffer solution	1 gram in 50 mL
4.5 pH acetate buffer	1 gram in 48 mL
6.8 pH phosphate buffer	1 gram in 44 mL
7.5 pH phosphate buffer	1 gram in 41 mL
Water only	1 gram in 45 mL

Permeability:
The Applicant did not submit permeability studies/data.

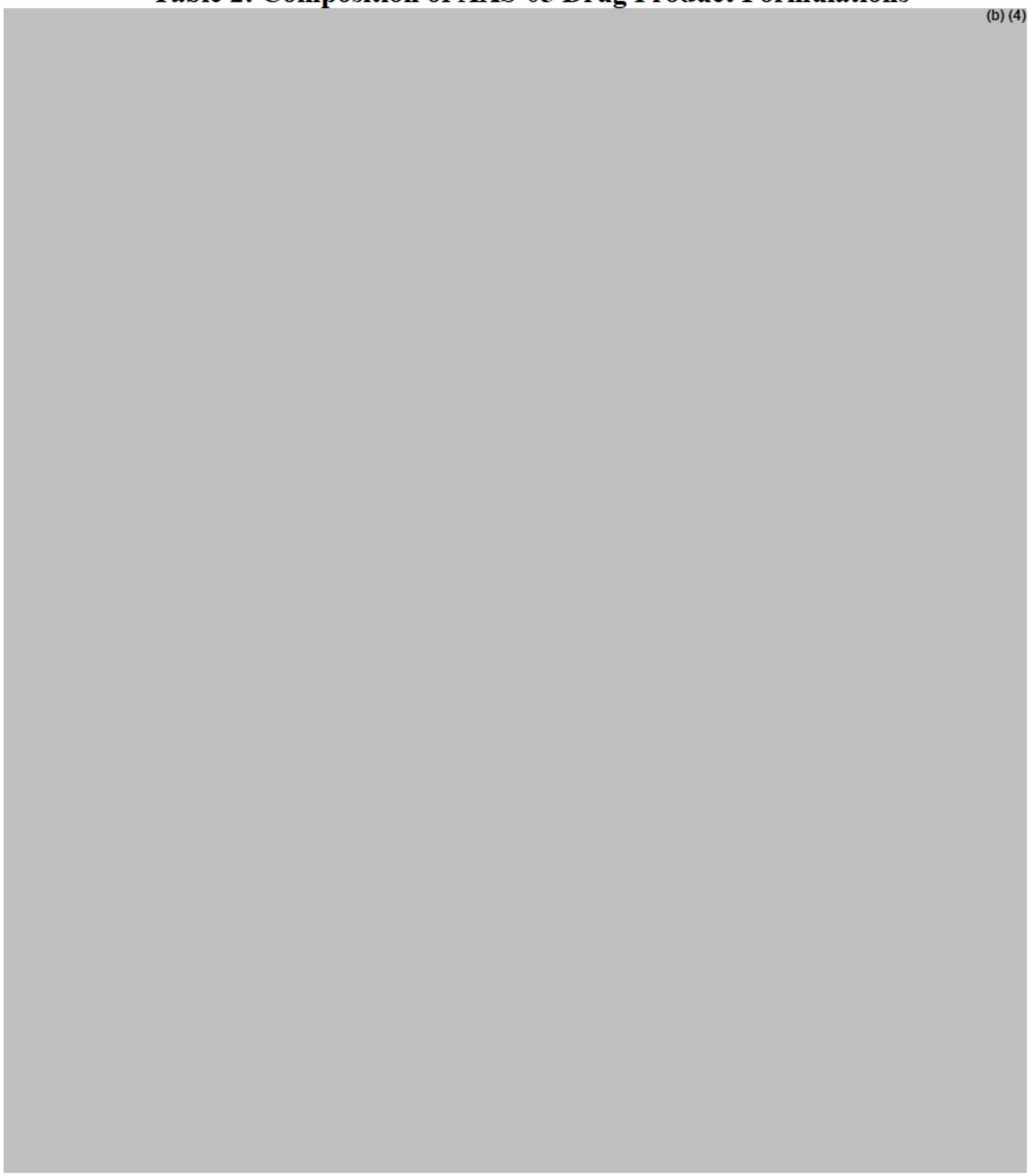
Dissolution: Please see the assessment in Section B.3.

B.2 COMPOSITION OF THE PROPOSED DRUG PRODUCT

AXS-05 is formulated into round, film-coated, bilayer tablets containing 45 mg dextromethorphan HBr and 105 mg bupropion HCl. The composition of the registration and intended commercial formulation (Version (b) (4)) is presented below along with the clinical drug product formulation (Version (b) (4)).

Table 2: Composition of AXS-05 Drug Product Formulations

(b) (4)



B.3 DISSOLUTION METHOD AND ACCEPTANCE CRITERIA

Assessment: *Inadequate*

Dissolution Method

The Applicant developed a single dissolution method for both APIs, i.e., extended-release bupropion HCl and immediate-release dextromethorphan HBr of the proposed FDC extended-release drug product. The proposed dissolution method conditions are provided below:

Table 3: Dissolution Method for Dextromethorphan and Bupropion in AXS-05 FDC Tablet

(b) (4)

[redacted]

Dissolution method development

(b) (4)

[redacted]

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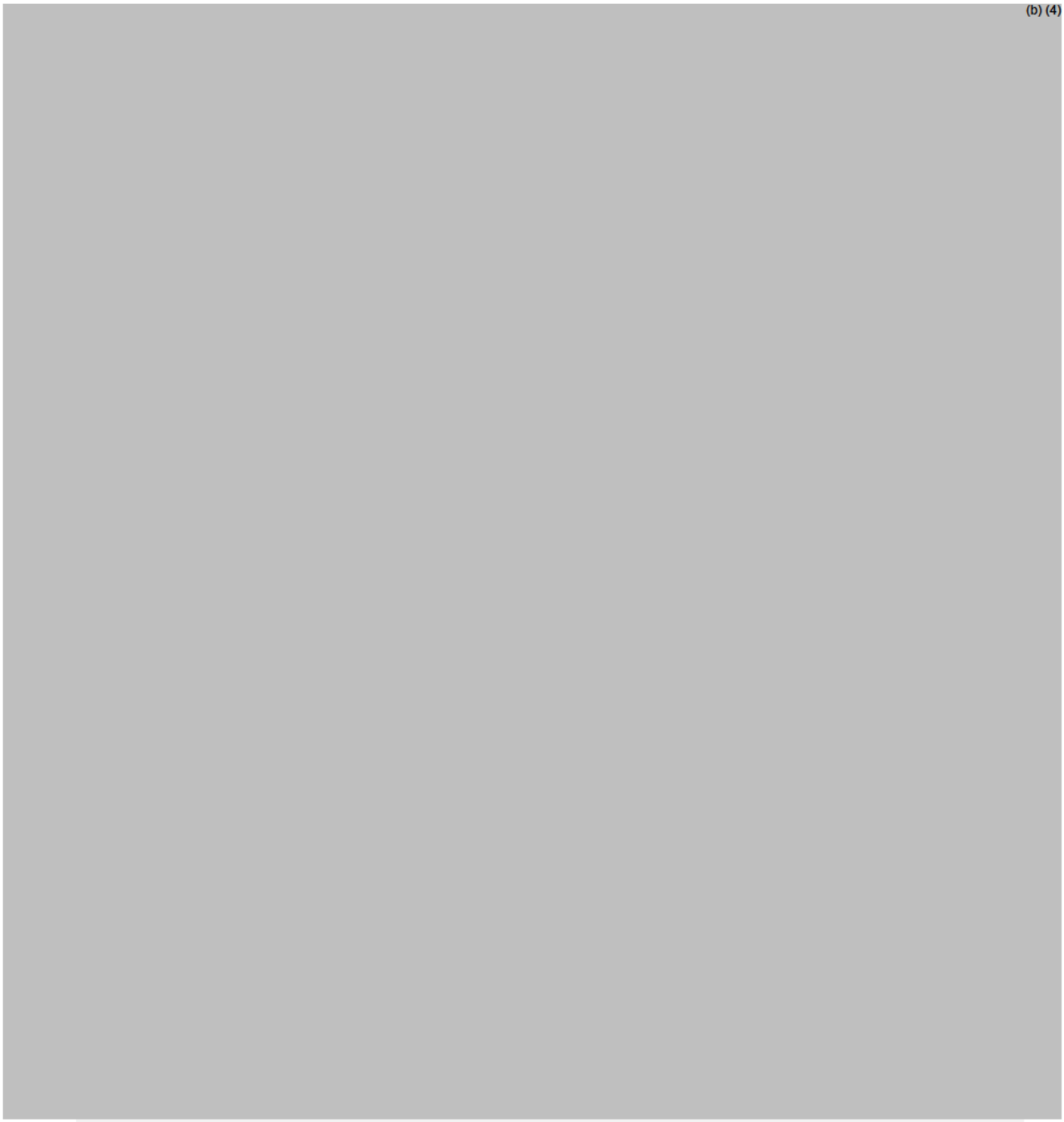


Discriminating ability of the dissolution method

The Applicant provided data for the discriminating ability of the dissolution method for both components of the FDC tablet in response to an IR (See IR1.4 in Appendix 1) and the details are provided in \\CDSESUB1\evsprod\nda215430\0010\m3\32-body-data\32p-drug-prod\axs-05\32p2-pharm-dev\pharmaceutical-development-2-14.pdf. The discriminatory power of the dissolution method was evaluated for potentially critical process parameters and material/ formulation properties. The following AXS-05 tablets were manufactured with intentional variations in formulation and process parameters to assess the discriminatory power of the dissolution method:

1. Variation in Formulation – Excipient Composition

(b) (4)

2. Variation in (b) (4) **Quantity**

(b) (4)

3.Variation in Processing Parameters

(b) (4)

Studies were performed on AXS-05 tablets from registration lot (bulk lot CFFXC, packaged registration lot CFTDV) and on tablets with intentional variations in formulation and process parameters (n=12 per variation). epresentative dissolution profiles are provided below.

Figure 6: BUP Reference and (b) (4) **Test Lots Dissolution**

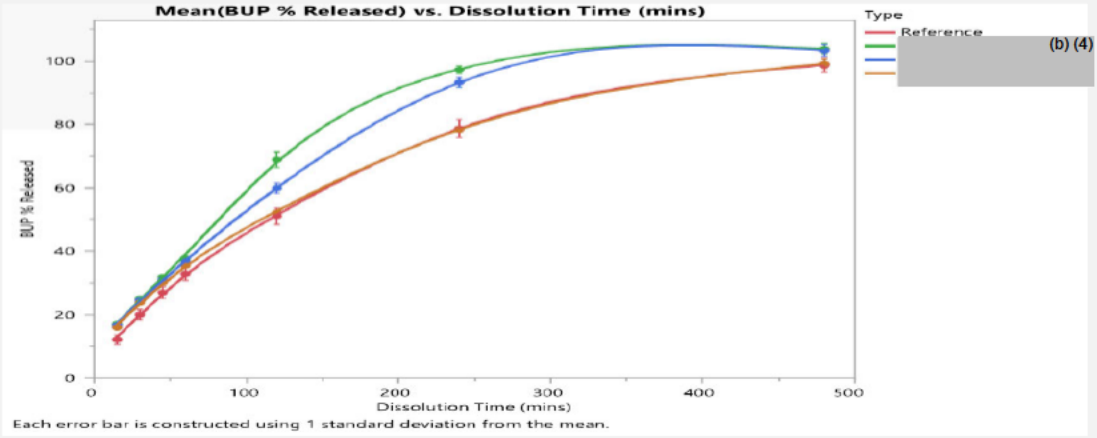


Figure 7: BUP Reference and (b) (4) Test Lots Dissolution

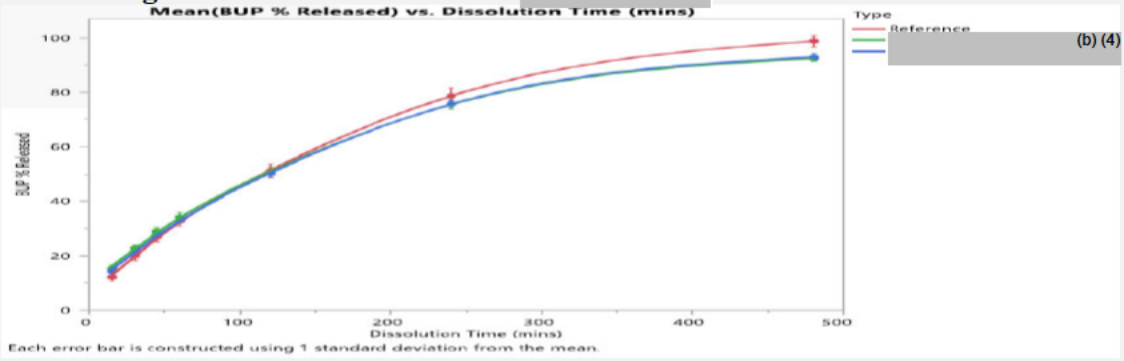


Figure 8: DM Reference and (b) (4) Test Lots DM Dissolution

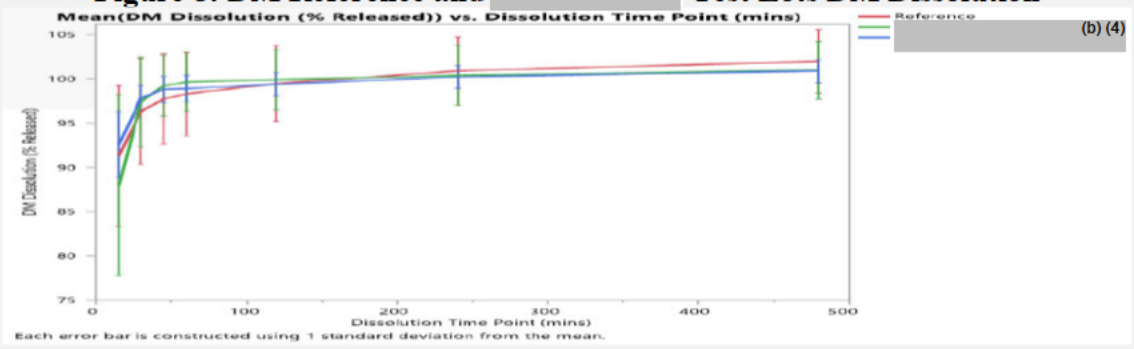


Figure 9: BUP Reference and (b) (4) Test Lots Dissolution

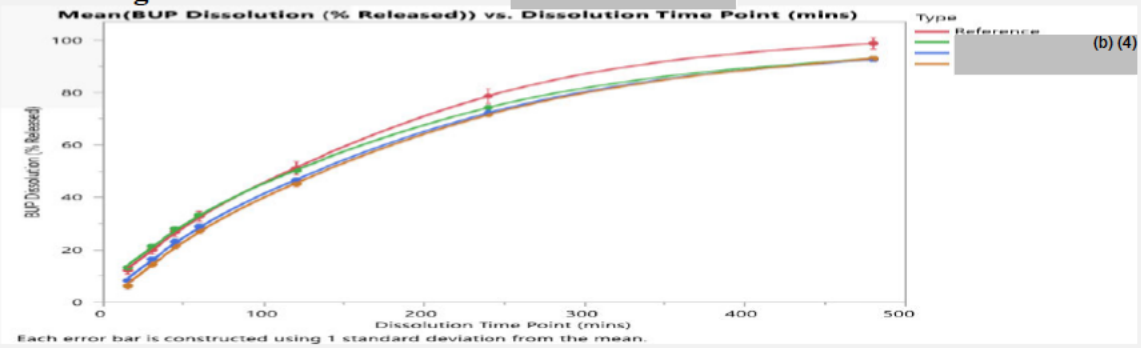
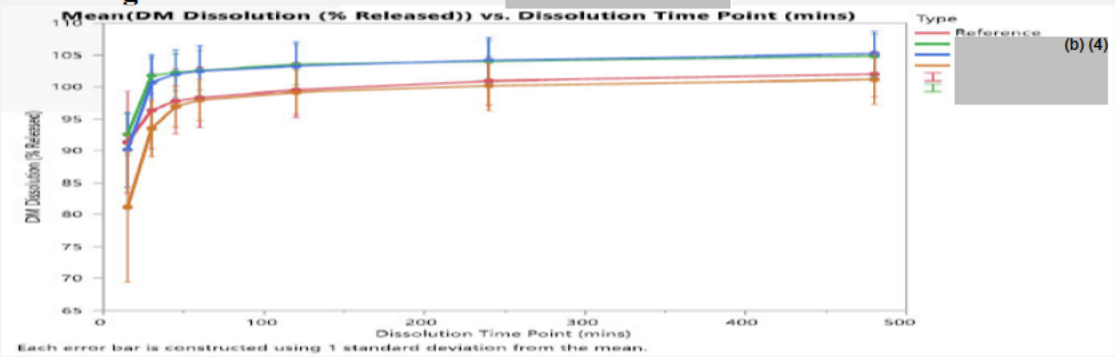


Figure 10: DM Reference and (b) (4) Test Lots Dissolution



The proposed single dissolution method could not discriminate the above critical quality attributes within the ranges tested, based on similarity testing, except for a borderline change (f2=49) in (b) (4) test batch for bupropion release. This Reviewer calculated and verified all the f2 values. No discriminating ability was demonstrated for dextromethorphan release and the data exhibited high variability in discriminating profiles of variant batches. The selected ranges of attributes for the test lots were also not within the recommended ranges (i.e., not within +/- (b) (4)%) except for the (b) (4). The Applicant noted that a T-test and Analysis of Variance with repeated measures was able to identify statistical and shape differences that were smaller than (b) (4)% between the reference and the test products. However, these measures are not acceptable to demonstrate the discriminating ability per the current Agency practice.

Based on the very limited discriminating ability of the method for both APIs, the Applicant was advised to develop separate dissolution methods with adequate discriminating ability for each component (Refer to IR1.4 in Appendix 1) during the review cycle. As noted earlier, the Applicant developed a single dissolution method for both bupropion and dextromethorphan components of the proposed drug product. Per the Agency's current practice, the Applicant should develop separate dissolution methods suitable for each API, except when a single method is adequately justified and deemed optimal (including satisfactory demonstration of discriminating ability of the method for each API). In response to the IR (refer to submission in seq 0010), the Applicant reiterated that the proposed method is suitable for dissolution evaluation of dextromethorphan and bupropion but also indicated that this issue will be addressed in the future, given the limited time for this priority submission. The Applicant will be requested to develop separate, optimal and discriminating dissolution method for each API.

Dissolution Acceptance Criteria

The Applicant proposed two sets of dissolution acceptance criteria for registration batches and commercial batches of bupropion and dextromethorphan as shown below.

Test (Release ☒ Stability ☒)	Method	Current Effective Acceptance Criteria	Proposed Commercial Acceptance Criteria
Dissolution – Dextromethorphan HBr	CTMLP-3899	NLT (b) (4)% at 30 minutes (Q = (b) (4)%)	NLT (b) (4)% at (b) (4) minutes (Q= (b) (4)%)
Dissolution – Bupropion HCl		Time Point / % Released	Time Point / % Released
		(b) (4) / (b) (4)% - (b) (4)%	(b) (4) / (b) (4)% - (b) (4)%
		2 hours / (b) (4)% - (b) (4)%	2 hours / (b) (4)% - (b) (4)%
		4 hours / (b) (4)% - (b) (4)%	4 hours / (b) (4)% - (b) (4)%
		8 hours / NLT (b) (4)%	8 hours / NLT (b) (4)%

Table below outlines the various lots of drug product (clinical, development, and registration batches) used in determining acceptance criteria per the Applicant.

Table 6: Drug Product Lots Used in Acceptance Criteria Evaluation

Bulk Drug Product Lot	XMHM	ZCVN	CCXWK	CDDZK#2	CFGCN	CFFXC	CFFXD	CFFXF
Date of Manufacture	Nov 2016	Feb 2018	Jul 2019	Aug 2019	Mar 2020	Apr 2020	Apr 2020	Apr 2020
Formulation Version	(b) (4)							
Packaged Lot	XPYK	ZPGP	CDDKN	CDDZK#2	CFKMC	CFTDV	CFTDW	CFTDX
Batch Size (Tablets)	(b) (4)							
Use	Phase 3 Clinical, Stability	Phase 3 Clinical	Phase 3 Clinical, Stability	Small-scale Trial, Stability	Large-scale Demo, Stability	Registration, Stability	Registration, Stability	Registration, Stability Clinical
Appearance	X	X	X	X	X	X	X	X
Identification (HPLC)	X	X	X	X	X	X	X	X
Identification (UV)					X	X	X	X
Potency Assay	X	X	X	X	X	X	X	X
Related Substances	X	X	X	X	X	X	X	X
RS (b) (4)	X	X	X	X	X	X	X	X
RS (b) (4)					X	X	X	X
Content Uniformity	X	X	X	X	X	X	X	X
Dissolution	X	X	X	X	X	X	X	X
(b) (4) Content	X	X	X	X	X	X	X	X
Microbial Limits	X	X	X		X	X	X	X

Demo = demonstration; HPLC = High Performance Liquid Chromatography; RS = related substance; UV = ultraviolet.

All dissolution data for dextromethorphan HBr and bupropion HCl for initial release and stability testing (at long-term condition 25°C/60% RH) of above development, clinical, and registration batches are provided in the links below:
\\CDSESUB1\evsprod\nda215430\0001\m3\32-body-data\32p-drug-prod\axs-05\32p8-stab\stability-summary-1.pdf
\\CDSESUB1\evsprod\nda215430\0015\m3\32-body-data\32p-drug-prod\axs-05\32p5-contr-drug-prod\32p56-justif-spec\justification-of-specifications.pdf

The dissolution profiles of these batches at release are presented in Figures 17 and 18.

The Applicant proposed different sets of dissolution acceptance criteria for registration batches and commercial batches of bupropion and dextromethorphan components, which is not acceptable from a regulatory perspective. In addition, the proposed acceptance criteria for either the registration batches or commercial batches are wider than recommended ranges and not acceptable.

During the review cycle, the Applicant was communicated to implement the acceptance criterion of "NLT (b) (4)% (Q) at 30 minutes" for dextromethorphan based primarily on the provided dissolution profile data of biobatch/registration batches, generated using the currently proposed dissolution method, as well as the Agency's current guideline for proper setting of the dissolution specification (Refer to IR2 in Appendix 1). In a response provided in sequence 0015, the Applicant agreed to the Agency recommendation.

For bupropion, the Applicant was recommended to implement the below acceptance criteria based on the provided dissolution profile data of biobatch/registration batches (Refer to IR3 in Appendix 1).

0.5 hr: (b) (4)%
2 hr: (b) (4)%
4 hr: (b) (4)%

8 hr: NLT (b)(4)%

In response (seq 0018), the Applicant revised the acceptance criteria only for the commercial batches, and not for the registration batches as requested. An IR (Refer to IR4 in Appendix 1) was again conveyed to the Applicant to implement the above interim acceptance criteria for both registration and commercial batches of bupropion for batch release and stability testing. In a response provided in sequence 0019, the Applicant agreed to the Agency's recommended acceptance criteria for both registration and commercial batches of bupropion and submitted a copy of the updated drug product specifications table.

Reviewer's Comment: Since the Applicant will be requested to develop separate optimal dissolution methods for each component of AXS-05 FDC product, the Applicant will be requested to propose new sets of dissolution acceptance criteria for each API of the drug product based on the newly generated data.

Note that no trend in drug release/dissolution was observed for the stability samples of bupropion. However, for dextromethorphan, the stability data of some clinical and registration batches showed a (b) (4) trend in dissolution. As shown in the figures below, the data for a clinical bulk batch, XMHM, shows (b) (4) dissolution at both 30, and (b)(4) minutes time point after 12-month testing.

Figure 11: Dextromethorphan HBr Dissolution at 30 Minutes (25°C/60%RH)

(b) (4)

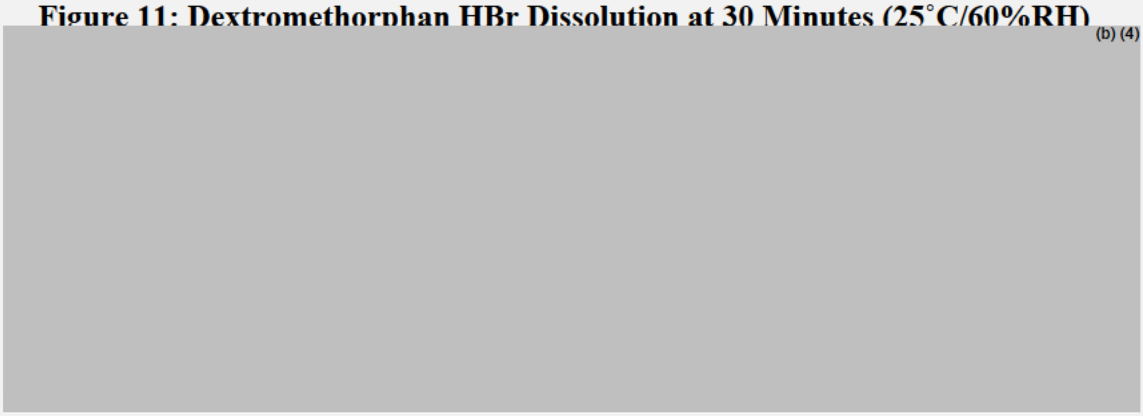
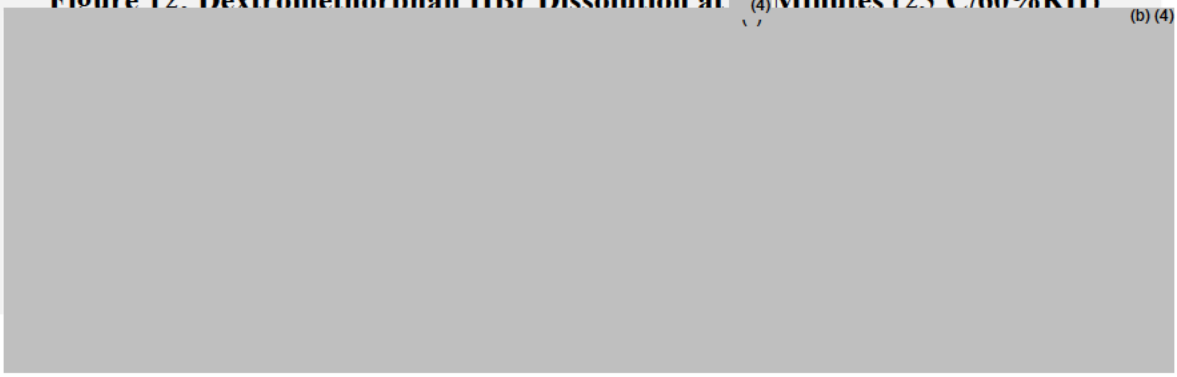


Figure 12: Dextromethorphan HBr Dissolution at (b)(4) Minutes (25°C/60%RH)

(b) (4)



B.4 MODIFIED RELEASE ORAL DRUG PRODUCTS – *In-Vitro Alcohol-Induced Dose Dumping*

Assessment: *Adequate*

The Applicant submitted the study information/data, per this Reviewer's request (see IR1.2 in Appendix 1), available in the link below:
\\CDSESUB1\evsprod\nda215430\0010\m3\32-body-data\32p-drug-prod\axs-05\32p2-pharm-dev\pharmaceutical-development-2-12.pdf

In vitro alcohol dose-dumping potential was investigated using 0.1 N HCl medium containing 0%, 5%, 10%, 20%, and 40% ethanol as recommended to the Applicant during the IND stage. The testing was conducted up to 8 hours.

For bupropion, exposure to 5% - 40% ethanol in 0.1 N HCl resulted in ethanol concentration-dependent but insignificant decreases in drug release profile compared to 0% ethanol in the first 2 hours as well as up to 8 hours, with similarity factor f2>50 for 5% - 20% ethanol and f2=47 for the 40% ethanol. The modified release characteristics was maintained through 8 hours. The dissolution profiles and f2 values are presented in figures and tables below.

Figure 13: Bupropion dissolution profiles in presence of alcohol for first 2 hours

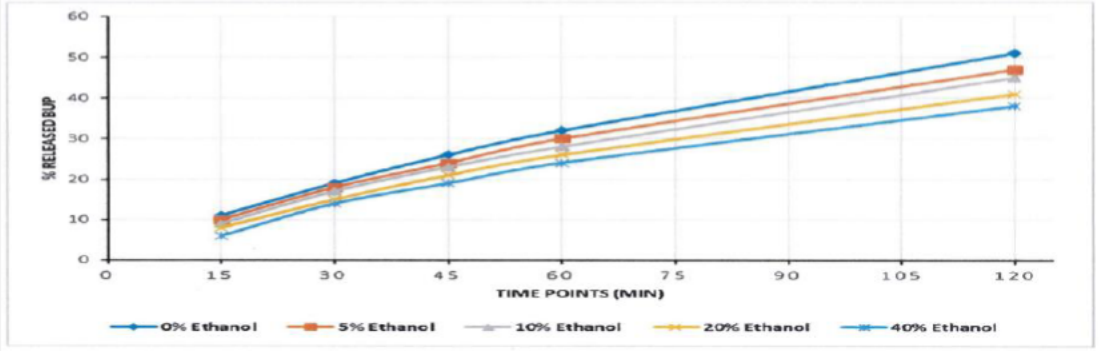


Figure 14: Bupropion dissolution profiles in presence of alcohol for 8 hours

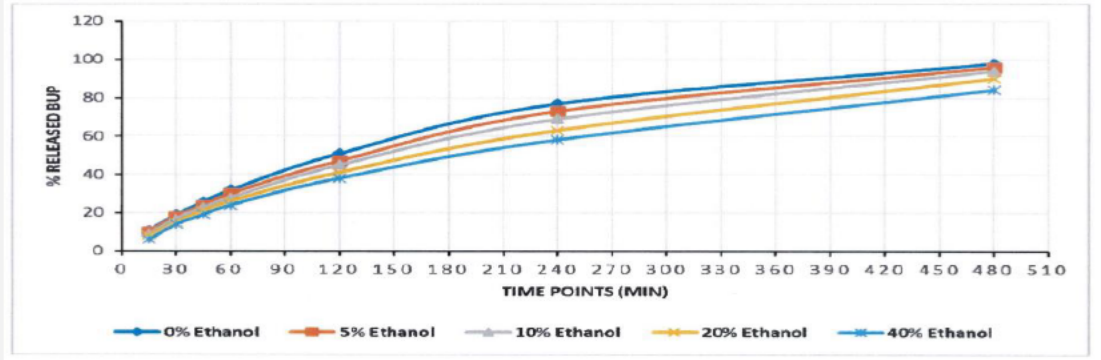


Table 7: Dissolution Profile Comparison for bupropion with Variation in Percentage of Alcohol

Time Points	R_t* (0% Ethanol)	T_t**			
		5%	10%	20%	40%
15 min	11	10	9	8	6
30 min	19	18	17	15	14
45 min	26	24	23	21	19
60 min	32	30	28	26	24
120 min	51	47	45	41	38
240 min	77	73	69	63	58
480 min	98	96	94	90	84
Similarity factor f2		**78**	**66**	**55**	**47**
Difference factor f1		**5**	**9**	**16**	**23**

*: R_t is mean dissolution value of the reference sample at time t (Tables 3 and 4)
**: T_t is mean dissolution value of the test sample at time t

For dextromethorphan, the dissolution profile data showed that drug releases were not significantly affected in the presence of 5% - 40% (v/v) alcohol, as illustrated in figures and tables below.

Figure 15: DM dissolution profiles with Variation in percentage of Alcohol first 2 hours

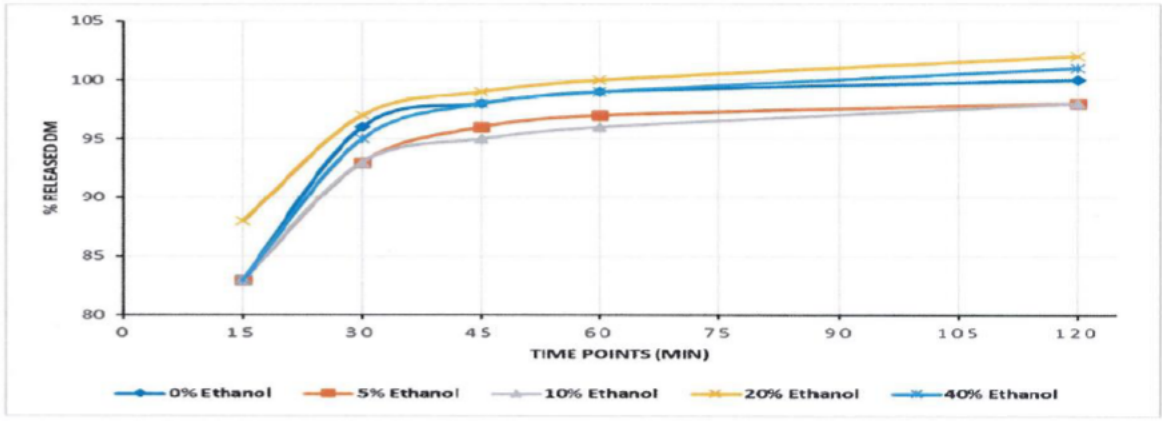


Figure 16: DM dissolution profiles with Variation in percentage of Alcohol for 8 hours

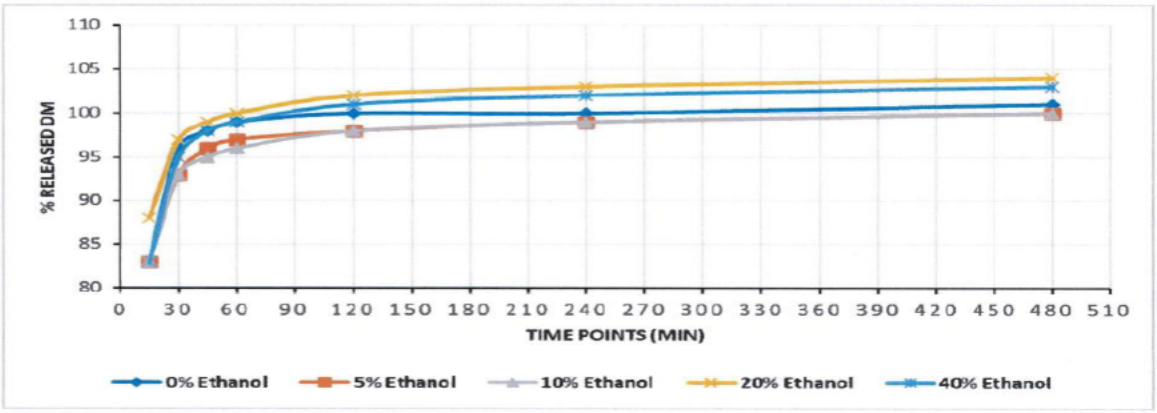


Table 8: Dissolution Profile Comparison for DM on Variation in Percentage of Alcohol

Time Points	R_t* (0% Ethanol)	T_t**			
		5%	10%	20%	40%
15 min	83	83	83	88	83
30 min	96	93	93	97	95
45 min	98	96	95	99	98
60 min	99	97	96	100	99
120 min	100	98	98	102	101
240 min	100	99	99	103	102
480 min	101	100	100	104	103
Similarity factor f2		**84**	**81**	**77**	**90**
Difference factor f1		**2**	**2**	**2**	**1**

*: R_t is mean dissolution value of the reference sample at time t (Tables 3 and 4)
**: T_t is mean dissolution value of the test sample at time t

In summary, alcohol had only a minimal effect on the dissolution of bupropion at the highest alcohol concentration (40% ethanol) with insignificant concentration-dependent decreases in dissolution and had no significant effect on the dissolution of dextromethorphan. The shape of the dissolution profiles for both compounds were similar when evaluating the first 2 hours, as well as the full 8-hour dissolution profile.

Reviewer's Comment:
The Applicant proposed in Section (b) (4) of the labeling that "(b) (4) (b) (4) (b) (4)."

B.5 EXTENDED RELEASE DOSAGE FORMS – *Extended Release Claim*
Assessment: *Adequate*

In response to an IR (see IR1.3 in Appendix 1), the Applicant provided information/data to support the extended-release claim of the proposed drug product, per criteria in 21 CFR 320.25(f). The Applicant noted that Module 3 documents refer to the bupropion component of AXS-05 as an extended-release formulation to comply with USP nomenclature; however, the product performs in a comparable manner to the reference drug, Wellbutrin (bupropion) SR.

The extended-release claim for the bupropion component of AXS-05 was based on data from two *in vivo* bioavailability studies (Study AXS-05-102 and Study AXS-05-106). In Study AXS-05-102, the pharmacokinetics of proposed and commercially available bupropion SR tablets (Zyban) was evaluated following a single dose and 8-days of daily dosing, while in Study AXS-05-106 (Cohort 4) the pharmacokinetics of the to-be-marketed formulation of AXS-05 was evaluated at the same dosing interval. A comparison of Day 1 and Day 8 pharmacokinetic parameters is provided in Table 9 and dose-adjusted pharmacokinetic parameters on Day 8 in Table 10 below.

Table 9: Bupropion Pharmacokinetic Parameters on Day 1 and 8 for AXS-05 (Study AXS-05-106) and Bupropion SR (Zyban) (Study AXS-05-102)

	Day 1		Day 8	
Parameter Mean (%CV)	**AXS-05 (Bupropion HCl 105 mg)**	**Bupropion SR (Zyban) (Bupropion HCl 150 mg)**	**AXS-05 (Bupropion HCl 105 mg)**	**Bupropion SR (Zyban) (Bupropion HCl 150 mg)**
AUC_{0-t} (ng*h/mL)	529.91 (24.97)	490.32 (31.34)	1796.89 (23.85)	1317.03 (43.05)
AUC_{0-12} (ng*h/mL)	441.16 (25.80)	490.41 (31.19)	663.55 (26.34)	798.75 (36.62)
AUC_{0-inf} (ng*h/mL)	597.69 (25.22)	NC	2169.26 (21.97)	1583.64 (50.09)
C_{max} (ng/mL)	83.31 (30.93)	75.22 (28.29)	87.95 (37.83)	103.38 (32.17)
C_{min} (ng/mL)	NC	NC	30.53 (26.37)	33.28 (43.99)
$T_{1/2el}$ (h)	7.16 (35.14)	3.44 (15.19)	19.71 (21.26)	13.58 (20.07)
T_{max} (h)[1]	2.977 (1.970-4.974)	3.01 (2-4)	2.974 (1.978-4.980)	3.00 (2-4)

[1]median (range); NC=not calculated

Table 10: Bupropion Pharmacokinetic Parameters for AXS-05 and Dose-Adjusted Bupropion SR (Zyban) on Day 8

Parameter on Day 8	**AXS-05 (Bupropion HCl 105 mg)**	**Bupropion SR (Zyban) (Dose Adjusted to Bupropion HCl 105 mg)**
AUC_{0-t} (ng*h/mL)	1796.89	921.92
AUC_{0-12} (ng*h/mL)	663.55	559.13
AUC_{inf} (ng*h/mL)	2169.26	1108.55
C_{max} (ng/mL)	87.95	72.37
C_{min} (ng/mL)	30.53	23.30

Data from these studies indicate that the pharmacokinetic profile for the bupropion component of AXS-05 is consistent with the pharmacokinetic profile for commercially available bupropion SR (Zyban). Pharmacokinetic data from eleven studies with AXS-05 in conjunction with *in vitro* dissolution data at release and on stability, rule out the occurrence of dose-dumping, with consistent delivery of bupropion with coefficients of variations for Cmax and AUC of approximately 25% on Day 1 and at steady-state. The data are deemed adequate to support the extended-release claim for the proposed product.

B.6 BRIDGING OF FORMULATIONS

Assessment: *Adequate*

Three formulations of AXS-05 (Versions (b) (4)) were developed and used in various clinical studies (Please refer to Table 2 for formulation compositions). The initial tablet formulation of AXS-05 (referred to as Version (b) (4) was developed and manufactured by (b) (4) (b) (4) Version (b) (4) is the clinical drug product, produced at (b) (4), following manufacturing transfer from (b) (4). Version (b) (4) is the registration drug product, and intended commercial formulation, produced at (b) (4).

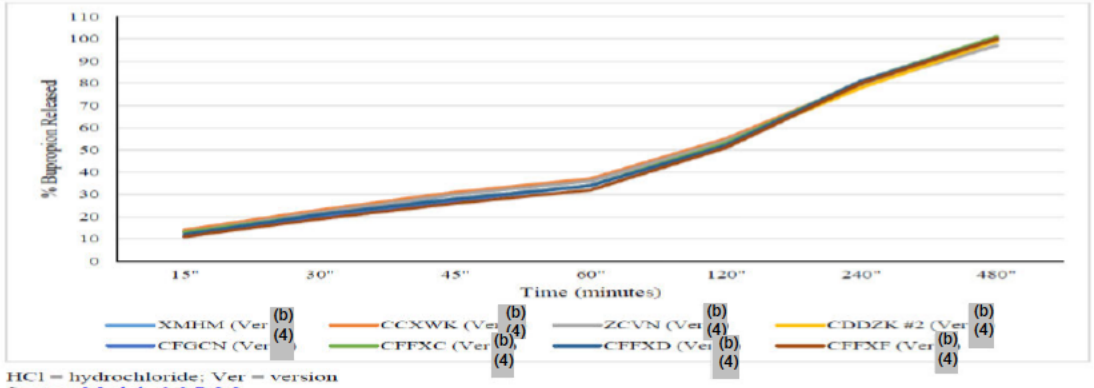
The composition of Versions (b) (4) are same. All clinical trial material for the Phase 2 trial AXS-05-MDD-201 and Phase 3 trial AXS-05-MDD-301 in MDD patients was manufactured

at (b) (4) using Version (b) (4) Version (b) (4) tablets were used in the Phase 1 food effect study and the long-term, open-label Phase 3 clinical trial. In this formulation, (b) (4)
(b) (4)

Initial formulation (Version (b) (4) shares the same composition as Version (b) (4) thus no bridging is necessary. To bridge Versions (b) (4) and Version (b) (4) tablet formulations, the Applicant provided comparative dissolution data as agreed during the Pre-NDA CMC-only meeting held on August 17, 2020. The dissolution data included comparative dissolution data for Version (b) (4) and Version (b) (4) drug product batches from batch release testing (in Module 3.2.P.2.2.) and additional dissolution studies in multi-media (Report no. AR/4062/001.00) as per the *Scale-Up and Post-Approval Changes (SUPAC-MR) Guidance*. In response to an IR (See IR1.1 in Appendix 1), the Applicant submitted complete dissolution profile data for all the lots.

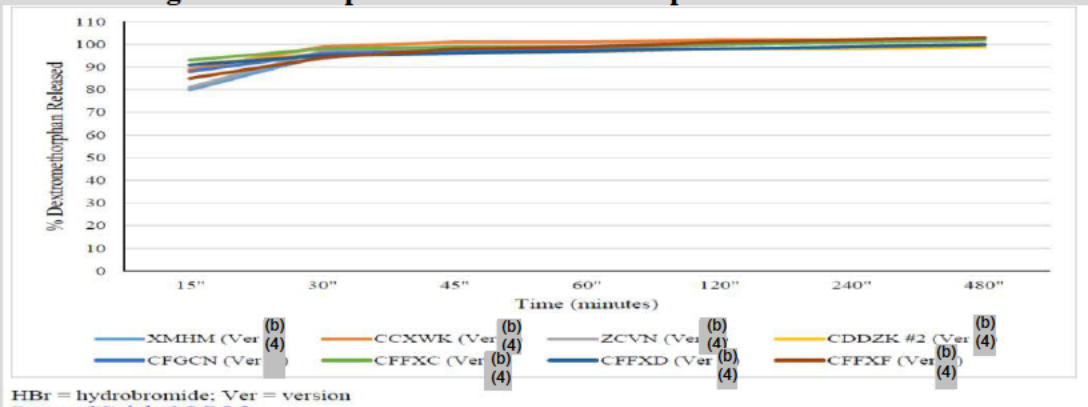
Batch release testing data for dissolution of bupropion HCl and dextromethorphan HBr for Version (b) (4) and Version (b) (4) demonstrates comparability between the two formulations as shown in figures below.

Figure 17: Comparison of Bupropion Hydrochloride Dissolution



HCl = hydrochloride; Ver = version
Source: Module 3.2.P.2.2

Figure 18: Comparison of Dextromethorphan HBr Dissolution



HBr = hydrobromide; Ver = version
Source: Module 3.2.P.2.2

Dissolution testing in three dissolution media: 0.1 N HCl, 0.1 M Acetate buffer at pH 4.5, and 0.1 M Phosphate buffer at pH 6.8 showed similarity between Version (b)(4) and both the old and new Version (b)(4) tablets, as demonstrated by f2 value more than 50 for bupropion HCl. For dextromethorphan, both Version (b)(4) and (b)(4) had greater than (b)(4)% percent dissolution in 30 minutes.

In vivo comparability of Version (b)(4) and Version (b)(4) tablets was also demonstrated by similar exposures of bupropion and dextromethorphan across separate multiple-dose Phase 1 pharmacokinetic (PK) studies, as summarized in Module 2.7.1 Section 3.1. The PK of the Version (b)(4) tablets was evaluated after 6 days of dosing in 3 multiple-dose studies (AXS-05-108, AXS-05-110, AXS-05-111); and the Version (b)(4) tablets were evaluated in 2 multiple-dose studies, one after 6 days of dosing (AXS-05-109) and one after 8 days of dosing (AXS-05-106). The Applicant noted that across each of these studies, the dextromethorphan and bupropion exposures were similar, demonstrating in vivo comparability of the tablets. These studies are under the purview of the OCP review team.

B. 7 BIOWAIVER REQUEST

Assessment: *Not Applicable*

The Applicant has not requested any biowaiver. There is only one strength of the FDC.

(b) (4)

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Ta-Chen Wu

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Valerie Amspacher

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VALERIE R AMSPACHER
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