CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

217338Orig1s000

PRODUCT QUALITY REVIEW(S)

NDA 217338

Executive Summary

1. Application/Product Information

NDA Number.	NDA 217338
Applicant Name	RB Health (US) LLC or Reckitt Benckiser LLC
Drug Product Name	Naproxen Na 110 mg, Dextromethorphan HBr 30 mg, Guaifenesin 600 mg extended-release tablet; conditionally approved proprietary name 'Mucinex 12 HR Cold & Fever Multi-Symptom'.
Dosage Form.	Tablet, extended release
Proposed Strength(s)	110 mg/30 mg/600 mg
Route of Administration	Oral
Maximum Daily Dose	440 mg/120 mg/2400 mg
Rx/OTC Dispensed	OTC
Proposed Indication	• Helps loosen phlegm (mucus) and thin bronchial secretions to rid the bronchial passageways of bothersome mucus and make cough more productive. • Temporarily relieves: - Cough due to minor throat and bronchial irritation as may occur with the common cold or inhaled irritants - The intensity of coughing - The impulse to cough to help you get to sleep - Minor aches and pains due to headache and common cold • Temporarily reduces fever
Drug Product Description	The drug product is a modified release bi-layer tablet consisting of a (b) (4) modified release layer (MR) debossed with 'Mucinex', (b) (4) , and a white immediate release layer (IR) (b) (4)

	[redacted] (b) (4)		
Co-packaged product information	N/A		
Device information:	N/A		
Storage Temperature/ Conditions	Store at 20-25°C (68-77°F). Avoid excessive heat above 40°C (104°F);		
Review Team	**Discipline**	**Primary**	**Secondary**
	Drug Substance	Stephanie Springer, Ph.D.	Sithamalli Chandramouli, Ph.D.
	Drug Product/ Labeling	Dhanalakshmi Kasi, Ph.D.	Danae Christodoulou, Ph.D.
	Manufacturing	Sydney Choi, Ph.D.	Aditi Thakur, Ph.D.
	Biopharmaceutics	Min Sung Suh, Ph.D.	Kevin Wei, Ph.D.
	Microbiology	N/A	
	Other (specify):	None	
	RBPM	Esther Jones	
	ATL	Swapan K De, Ph.D.	
Consults	None		

2. Final Overall Recommendation on Quality Perspective-

Approval

4. Basis for Recommendation:

a. Summary of Rationale for Recommendation:

Regarding quality aspects of the application the drug substance, drug product, biopharmaceutics, process, and facility sections are reviewed during the review cycle, and found adequate to support the approval of the application. The drug product has been granted a shelf life of 36 months in all container closure configurations.
In brief, CMC review has no outstanding issues and adequate to support the NDA.

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

Recommendation by Subdiscipline:

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

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

5. Life-Cycle Considerations

Established Conditions per ICH Q12: No
Comments:

Comparability Protocols (PACMP): No
Comments:

Additional Lifecycle Comments:

None

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

CHAPTER IV: LABELING

IQA NDA Assessment Guide Reference

Assessment of Product Quality Related Aspects:

This is an OTC product. The applicant provided carton, container label and DFL. Package insert is not provided. The information provided below is captured from the NDA 217338 application and drug product review.

Items Provided in the NDA:

Item	Information Provided in the NDA	Assessor's Comments
Proprietary name	Mucinex® 12 HR COLD & FEVER MULTI-SYMPTOM	New proprietary name request was submitted on 12/18/23.
Established name(s)	Naproxen Sodium, Dextromethorphan HBr, Guaifenesin	Adequate
Route(s) of administration	Oral	Adequate
Dosage Forms and Strengths		
Summary of the dosage form(s) and strength(s) in metric system.	Dextromethorphan HBr 30 mg Guaifenesin 600 mg Naproxen sodium 110 mg	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	N/A
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other	N/A	N/A

package terms include pharmacy bulk package and imaging bulk package.		

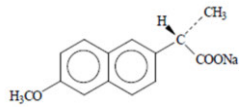
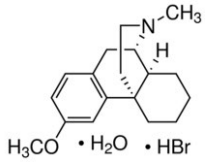
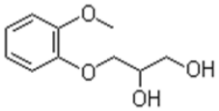
Section 2 (DOSAGE AND ADMINISTRATION)

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

Section 3 (DOSAGE FORMS AND STRENGTHS)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Extended Release Tablet	Adequate
Strength(s) in metric system	Naproxen Sodium 110 mg Dextromethorphan HBr 30 mg Guaifenesin 600 mg	Adequate
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance	Each extended-release tablet contains: Naproxen Sodium 110 mg (101 mg of Naproxen) Dextromethorphan HBr 30 mg (22 mg of Dextromethorphan) Guaifenesin 600 mg	Adequate
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting	Section 3.2.P.1	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	N/A
For injectable drug products for parental administration, use appropriate labeling term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.	N/A	N/A

Item	Information Provided in the NDA	Assessor's Comments
DESCRIPTION section		
Proprietary Name Established name(s)	Mucinex 12 HR Cold & Fever Multi-Symptom Naproxen Sodium, Dextromethorphan HBr, Guaifenesin Extended-Release Tablet	Adequate
Dosage form(s) and route(s) of administration	Extended-Release Tablet, Oral	Adequate
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	Each (b) (4) contains Naproxen Sodium 110 mg ((b) (4) mg of naproxen) Dextromethorphan HBr 30 mg ((b) (4) mg of Dextromethorphan)	Adequate
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names	Croscarmellose Sodium, FD&C Red No. 40, Hydroxyethyl Cellulose, Hypromellose, Magnesium Stearate, Microcrystalline Cellulose, Polyethylene Glycol, Sodium Bicarbonate, Sodium Lauryl Sulfate	Adequate
For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	N/A	N/A
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	The drug product does not contain alcohol	N/A
Statement of being sterile (if applicable)	This is a non-sterile product	N/A

Pharmacological/ therapeutic class	Naproxen Sodium - Antipyretic, anti-inflammatory, and analgesic Dextromethorphan HBr - Antitussive Guaifenesin - Expectorant	Adequate
Chemical name, structural formula, molecular weight	Naproxen Sodium  C14H13NaO3 252.25 Dextromethorphan HBr  C18H25NO, HBr, H2O 370.3 Guaifenesin  C10H14O4 198.2	Adequate
If radioactive, statement of important nuclear characteristics	N/A	N/A
Other important chemical or physical properties (such as pKa or pH)	N/A	Adequate
If radioactive, statement of important nuclear characteristics.	N/A	N/A

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

<table>
<tr><th>Item</th><th>Information Provided in the NDA</th><th>Assessor's Comments</th></tr>
<tr><td colspan="3">HOW SUPPLIED/STORAGE AND HANDLING section</td></tr>
<tr><td>Available dosage form(s)</td><td>Extended-Release Tablets</td><td>Adequate</td></tr>
<tr><td>Strength(s) in metric system</td><td>Naproxen Sodium 110 mg, Dextromethorphan HBr 30 mg, and Guaifenesin 600 mg</td><td>Adequate</td></tr>
<tr><td>Available units (e.g., bottles of 100 tablets)</td><td>Table 3.2.P.7.1 – 1 Proposed Pack Sizes / Blister Cards
<table><tr><th>Pack Size</th><th>Blister Card x Tablet Count</th></tr><tr><td>4</td><td>1 x 4</td></tr><tr><td>8</td><td>1 x 8</td></tr><tr><td>16</td><td>2 x 8</td></tr><tr><td>32</td><td>4 x 8</td></tr><tr><td>60</td><td>6 x 10</td></tr></table></td><td>Adequate</td></tr>
<tr><td>Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number</td><td>The description has been provided in the NDA.</td><td>Adequate</td></tr>
<tr><td>Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"</td><td>N/A</td><td>N/A</td></tr>
</table>

For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	N/A	N/A

Item	Information Provided in the NDA	Assessor's Comments
Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to "Dispense in original container," provide reason why (e.g., to protect from light or moisture, to maintain stability, etc.)	Store at 20-25°C (68-77°F). Avoid excessive heat above 40°C (104°F). 2.12	Adequate
If the product contains a desiccant, ensure the size and shape differ from the dosage form and desiccant has a warning such as "Do not eat."	N/A	N/A
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Store at 20-25°C (68-77°F).	The storage condition is supported by stability data and is acceptable.

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	N/A
Include information about (b) (4) packaging	(b) (4) blister cards sealed with foil backing and packed in a paperboard carton.	Adequate

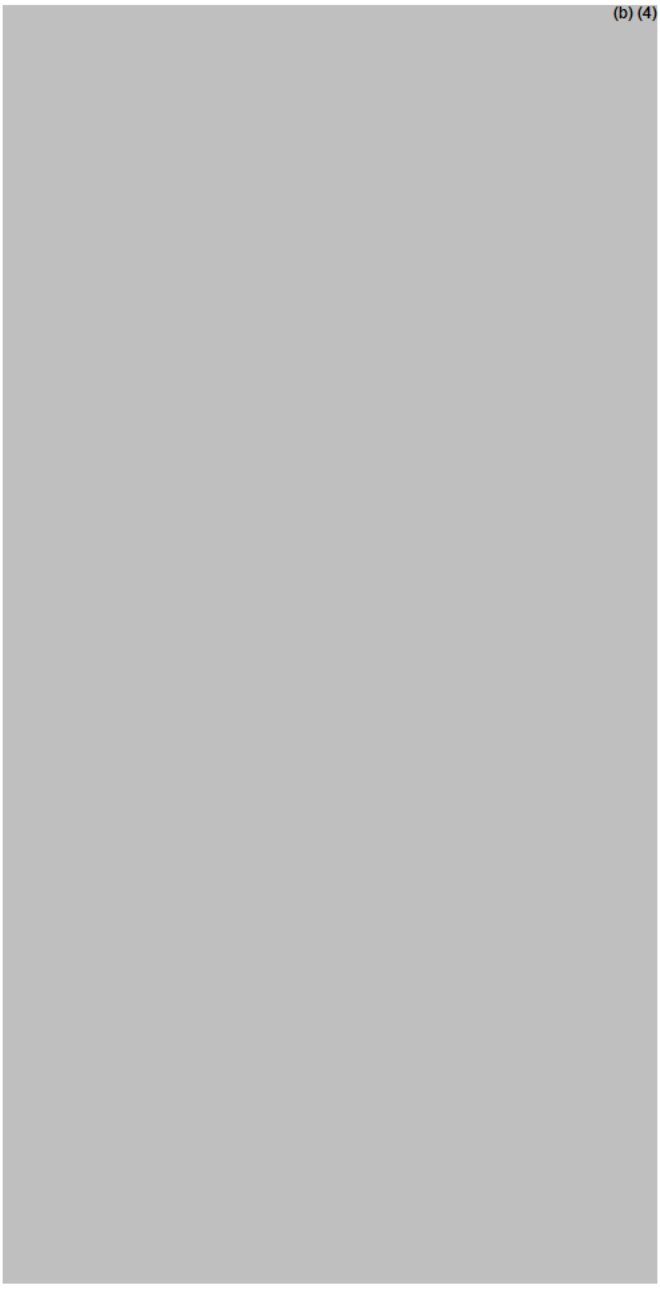
Item	Information Provided in the NDA	Assessor's Comments
Manufacturing Information After Section 17		
Name and location of business (street address, city, state, and zip code) of the manufacturer, distributor, and/or packer	(b) (4) by: Reckitt Benckiser Healthcare International Ltd.	Adequate

1.0 PATIENT LABELING

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

N/A

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page



Assessment of Carton and Container Labeling: *Adequate.*

The product labels have all the relevant information in accordance with regulatory requirements from a CMC perspective. Labeling will be finalized through OND during labeling negotiations with the applicant.

ITEMS FOR ADDITIONAL ASSESSMENT

None.

Overall Assessment and Recommendation:

The product labels are acceptable from a CMC perspective.

Primary Labeling Assessor Name and Date: Dhanalakshmi Kasi., 05/22/2024

Secondary Assessor Name and Date (and Secondary Summary, as needed): Danae Christodoulou 05/22/2024

Dhanalakshmi Kasi

Digitally signed by Dhanalakshmi Kasi
Date: 5/29/2024 10:56:44AM
GUID: 53150dea000054615f30e13bde0d487c

Danae Christodoulou

Digitally signed by Danae Christodoulou
Date: 5/29/2024 11:32:35AM
GUID: 5050dd27000012a4c69bfc70b47660b7

CHAPTER VI: BIOPHARMACEUTICS

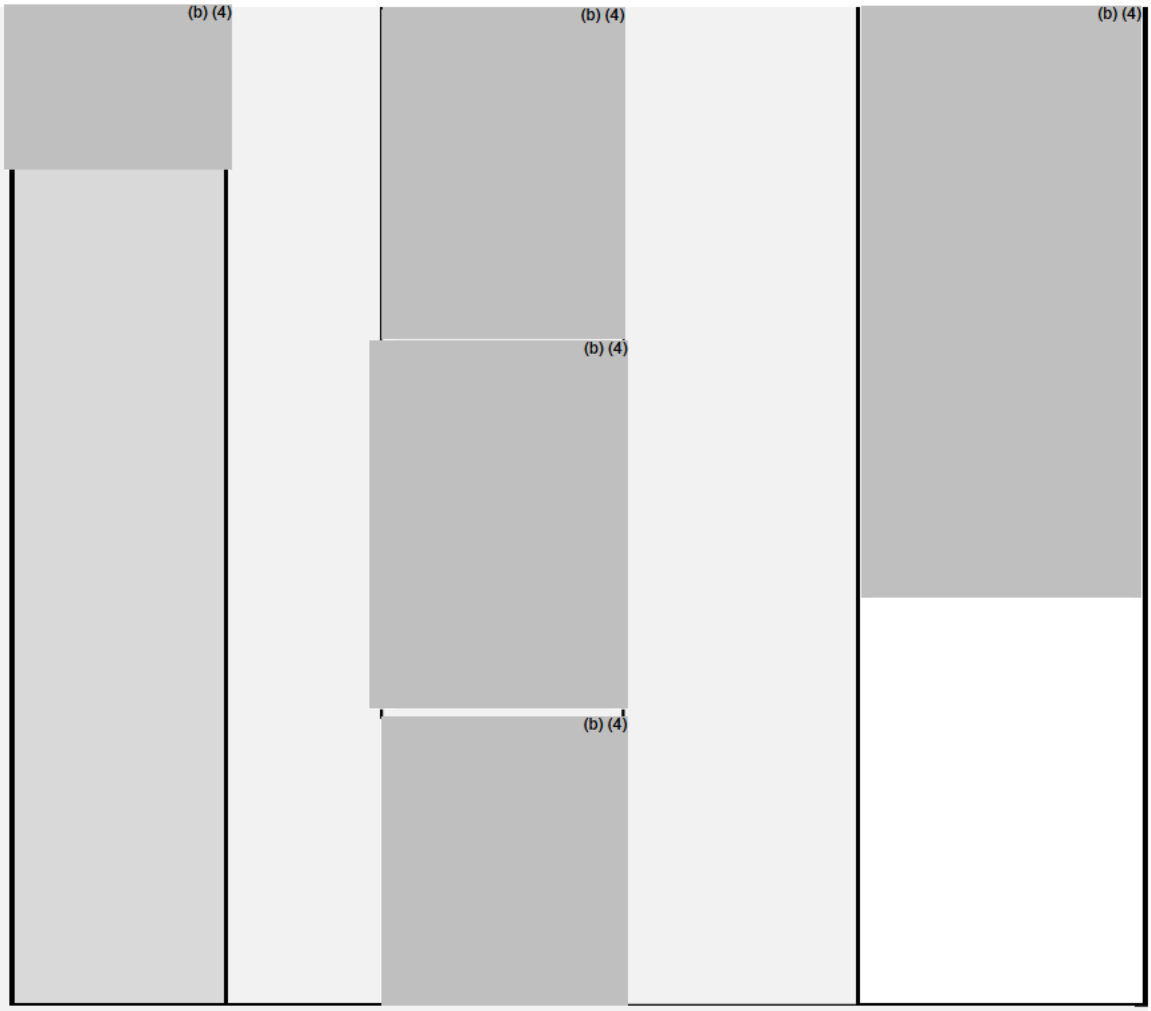
For more details about the items in this template, please see Chapter VI (Biopharmaceutics) of the NDA IQA Guide

Product Information	
NDA Number	217338
Assessment Cycle Number	1
Drug Product Name/ Strength	Naproxen Sodium 110 mg, Dextromethorphan HBr 30 mg, Guaifenesin 600 mg Extended-Release Tablet
Route of Administration	Oral
Applicant Name	RB Health
Therapeutic Classification/ OND Division	Division of Non-Prescription Drug 1
LD/RS Number	NDA 021620 and 020204, 505 (b)(2)
Proposed Indication	Pain reliever/fever reducer, cough suppressant, and expectorant

Assessment Recommendation: **Adequate**

Assessment Summary:

CQAs	Initial Risk Ranking	Comments	Updated Risk Ranking after Assessment Cycle #1	Comments
(b) (4)	High	(b) (4)	N/A	(b) (4)



The Applicant, RB Health, submitted this 505(b)(2) NDA for a modified release bilayer tablet containing guaifenesin 600 mg, dextromethorphan HBr 30 mg, and naproxen sodium 110 mg for over the counter (OTC) use to relieve multiple symptoms of upper respiratory infections, most notably from the common cold (b) (4).

Compared to the currently approved OTC products containing the same ingredients: Mucinex® DM (600 mg guaifenesin / 30 mg dextromethorphan HBr) and Aleve® (220 mg naproxen sodium), the proposed drug product is comprised of an immediate release (IR) portion/layer (b) (4), and an extended-release (ER) layer (b) (4). This proposed fixed-dose combination (FDC) product is proposed to be taken as two tablets every 12 hours by adults and children 12 years and older. It is intended for the OTC use of relieving multiple self-diagnosable respiratory symptoms of an upper respiratory infection that include cough, chest congestion, fever, and pain.

A bioequivalence study involving single doses under fasted and fed conditions was conducted comparing the active pharmaceutical ingredients (APIs) in both the test product and the listed drug products (RB5-US-1505). This study, denoted as an open-label, single-dose, randomized 4-period, 4-sequence,

crossover, relative comparative bioavailability study, evaluated the drug PK compared to the relied upon Listed Drug (LD) products, Mucinex® DM and Aleve® tablets under fasted and fed states.

The composition of the proposed drug product is shown in Table below.

Compositions of immediate- and modified-release layers

Each immediate release layer contains:

Name of Ingredient	Amount per Unit (mg/layer)	%w/w of Immediate release layer	Function	Quality Standards
(b) (4)				
Total IR layer weight (mg)	(b) (4)			

USP: Complies with the relevant current monograph in the US Pharmacopoeia
NF: Complies with the relevant current monograph in the National Formulary

Each modified release layer contains:

Name of Ingredient	Quantity (mg/layer)	%w/w of Modified release layer	Function	Quality Standards
(b) (4)				
Total MR layer weight (mg)	(b) (4)			
	(b) (4)			

USP: Complies with the relevant current monograph in the US Pharmacopoeia
NF: Complies with the relevant current monograph in the National Formulary
(b) (4)

This Biopharmaceutics review was focused on the following aspects:

Quality control (QC) dissolution method and acceptance criterion:

The Applicant originally proposed a dissolution method of USP Apparatus 2 (paddle) at (b) (4) rpm in 900 mL of 50 mM sodium phosphate buffer, pH 6.8 at 37°C for the QC of the proposed drug product. The originally proposed method was not found acceptable because there was inadequate data/information to support 1) the use of a (b) (4) rpm and 2) the discriminating ability of the proposed dissolution method. Therefore, the Applicant was requested to further optimize the dissolution parameters (e.g., low agitation speed) and evaluate the discriminating ability of the selected method via Information Request 1 (IR#1). In response to the IR#1 date 04/17/2024, the Applicant further evaluated the dissolution parameters and discriminating ability of the proposed method. The submitted dissolution data indicated that complete dissolution was observed with the use of a low paddle speed of 50 rpm that reflecting a better discriminating ability towards the identified CFVs ((b) (4)) and CPPs ((b) (4)). Therefore, the Applicant was recommended to provide additional dissolution data and information of the clinical and newly manufacturing method development batches using USP 2 (paddle) at 50 rpm in 900 mL of 50 mM sodium phosphate buffer (pH 6.8) via IR#2. Based on dissolution data and information provided in response to IR#2 dated 05/06/2024, the following

dissolution method and acceptance criteria were found more appropriate for the QC of the proposed drug product.

Dissolution	Method	Acceptance criteria
Dextromethorphan HBr	USP 2 (Paddle) at 50 RPM 900 mL of 50 mM Sodium Phosphate, pH 6.8 at 37°C	1 hour: (b) (4)% 2 hours: (b) (4)% 6 hours: (b) (4)% 12 hours: NLT (b) (4)%
Guaifenesin		1 hour: (b) (4)% 2 hours: (b) (4)% 6 hours: (b) (4)% 12 hours: NLT (b) (4)%
Naproxen Sodium		Q= (b) (4)% in 30 minutes

The Applicant was recommended to implement the above dissolution method and acceptance criteria for the QC of the proposed drug product via IR#3. In the response to the IR#3 dated 05/10/2024, the Applicant accepted the recommended dissolution method and acceptance criteria and revised the relevant sections accordingly. The Applicant's response and revised the dissolution method and acceptance criteria are found adequate.

Product Bridging:
Based on the information provide (response to IR#2 dated 05/06/2024), there is no significant change in the formulation, manufacturing process, manufacturing site or batch size among the pivotal clinical batches, registration and primary stability batches, and the proposed to-be-marketed product. Therefore, no additional bridging is warranted.

Overall, from a Biopharmaceutics perspective, NDA 217338 for Naproxen Sodium 110 mg, Dextromethorphan HBr 30 mg, Guaifenesin 600 mg Extended-Release Tablet is **adequate** and recommended for **Approval**.

List of Submissions Being Assessed:

Document(s) Assessed	Date Received
Orig-1 NDA	**09/29/2023**
Response to IR#1[1]	**04/17/2024**
Response to IR#2[2]	**05/06/2024**
Response to IR#3[3]	**05/10/2024**

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

[1] \\CDSESUB1\EVSPROD\nda217338\0016\m1\us\111-info-amend\resp-20240226.pdf
[2] \\CDSESUB1\EVSPROD\nda217338\0017\m1\us\111-info-amend\resp-20240419.pdf
[3] \\CDSESUB1\EVSPROD\nda217338\0018\m1\us\111-info-amend\resp-20240507.pdf

Concise Description of Outstanding Issues *(list bullet points with key information and update as needed)*: None

B.1 BCS DESIGNATION

Assessment: *Adequate*

Solubility: Low

According to the Applicant, guaifenesin is a high solubility drug substance classified as a BCS 1, and dextromethorphan HBr and naproxen sodium are low solubility drug substances classified as a BCS 2. The Applicant investigated the sink conditions to confirm the proposed dissolution medium (900 mL of 50 mM sodium phosphate buffer, pH 6.8) is capable of dissolving three times more than the proposed dose amount of the three APIs. The results indicate that all APIs meet sink conditions in the proposed medium (Table 1).

Table 1. Sink study results (dissolved %)

Active / Vessel	Guaifenesin (12 Hours)	Dextromethorphan (12 hours)	Naproxen Sodium (6 hours)	Naproxen Sodium (12 hours)
1	(b) (4)			
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
Mean				
%RSD	4	5	4	4

Permeability: High

No permeability data of the three APIs were provided but based on references, the APIs are highly permeable.

Dissolution: See "B.2 DISSOLUTION METHOD AND ACCEPTANCE CRITERIA"

B.2 DISSOLUTION METHOD AND ACCEPTANCE CRITERIA

Assessment: *Adequate*

- **Drug Product Background**

The proposed drug product is a FDC bilayer tablet containing guaifenesin 600 mg, dextromethorphan HBr 30 mg, and naproxen sodium 110 mg that is comprised of an IR layer (b) (4) and an ER layer (b) (4).

- **Dissolution Method Development**

Selection of Dissolution Conditions

(b) (4)

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

(b) (4)

[redacted]

➢ **Dissolution Variability**

Variabilities in the dissolution data meet the recommendations (%CV < (b) (4) % at all timepoints).

➢ **Dissolution Acceptance criteria**

Based on the dissolution data (Table 7) from the clinical batch provided in response to IR#2 dated 05/06/2024, the following dissolution acceptance criteria were recommended to the Applicant via IR#3 for the QC of the proposed drug product via IR#3 (Table 8).

Table 8. Proposed and recommended acceptance criteria

API	Proposed	Recommended
Dextromethorphan HBr	1 hour: (b) (4) %	1 hour: (b) (4) %

	2 hours: (b) (4) % 6 hours: (b) (4) % 12 hours: NLT (b) (4) %	2 hours: (b) (4) % 6 hours: (b) (4) % 12 hours: NLT (b) (4) %
Guaifenesin	1 hour: (b) (4) % 2 hours: (b) (4) % 6 hours: (b) (4) % 12 hours: NLT (b) (4) %	1 hour: (b) (4) % 2 hours: (b) (4) % 6 hours: (b) (4) % 12 hours: NLT (b) (4) %
Naproxen Sodium	1 hour: NLT (b) (4) % 6 hours: NLT (b) (4) %	Q= (b) (4) % in 30 minutes

In the response to the IR#3 dated 05/10/2024, the Applicant accepted the recommended dissolution acceptance criteria and revised the relevant sections accordingly. The Applicant's response and revised the dissolution acceptance criteria are found adequate.

B.3 CLINICAL RELEVANCE OF DISSOLUTION METHOD & ACCEPTANCE CRITERIA *(e.g., IVIVR, IVIVC, In Silico Modeling, small scale in vivo)*

Assessment: *N/A*

No IVIVC/R, in silico modeling or small scale in vivo data are submitted to support the proposed dissolution method or acceptance criteria.

B.5 MODIFIED RELEASE ORAL DRUG PRODUCTS – *In-Vitro Alcohol Dose Dumping*

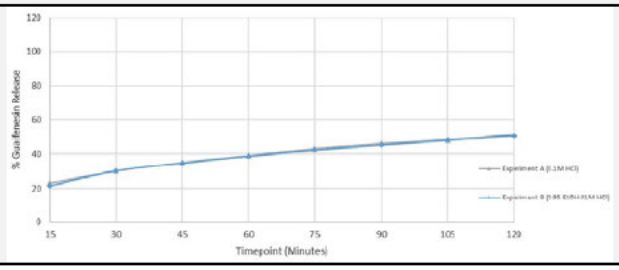
Assessment: *Adequate*

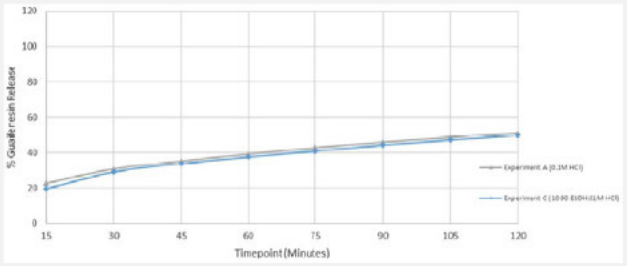
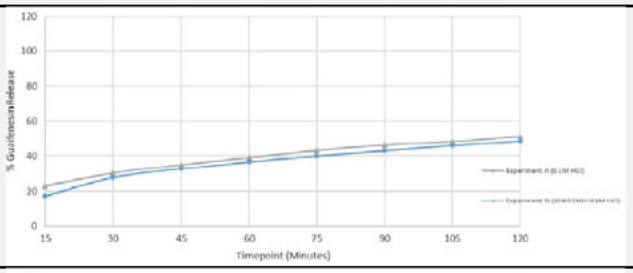
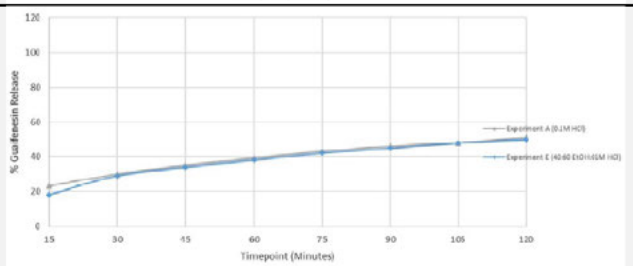
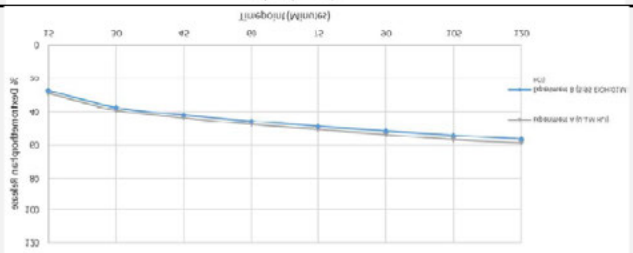
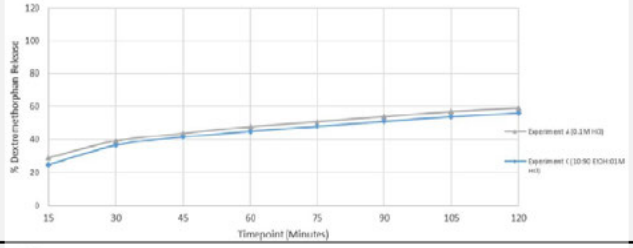
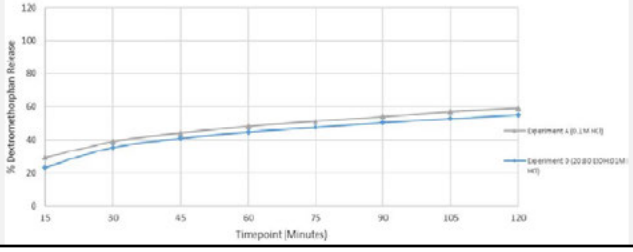
In vitro alcohol dose dumping studies for the proposed drug product were evaluated in two different media [0.1N HCl and 50 mM sodium phosphate buffer, pH 6.8 (QC)] with the addition of ethanol (5, 10, 20 and 40%).

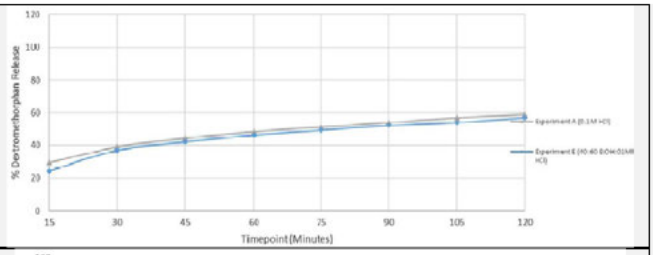
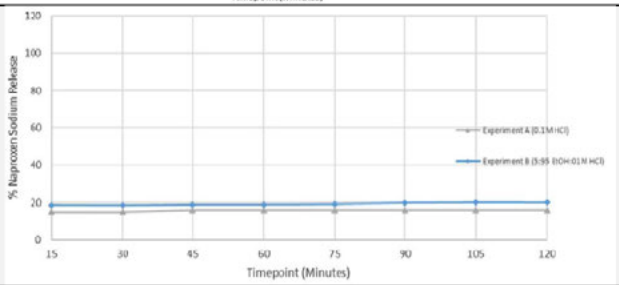
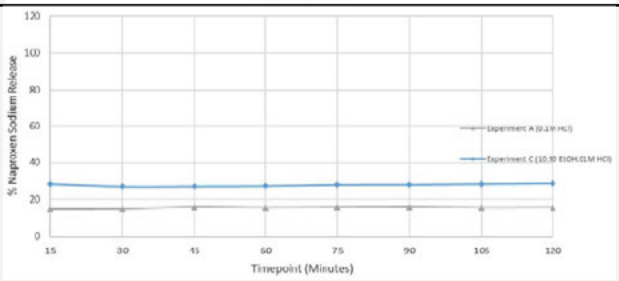
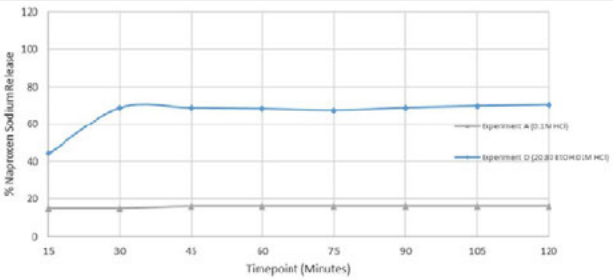
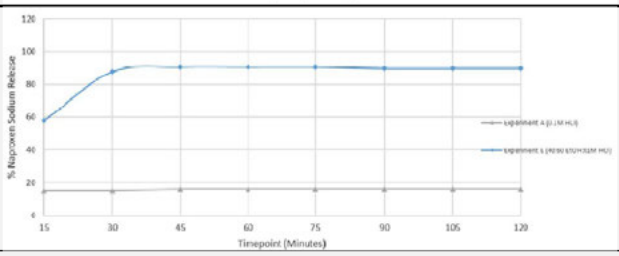
- **0.1N HCl with 5, 10, 20 and 40% ethanol**

The dissolution profiles of naproxen sodium showed a significant impact of alcohol content in 0.1N HCl media due to its limited solubility, whereas no alcohol dose dumping was observed on dissolution of guaifenesin and dextromethorphan HBr (Table 9).

Table 9. Comparative dissolution profiles of guaifenesin, dextromethorphan HBr and naproxen sodium in 0.1N HCl with alcohol at 5, 10, 20 and 40%

API	0.1N HCl with alcohol	
Guaifenesin	**5%**	

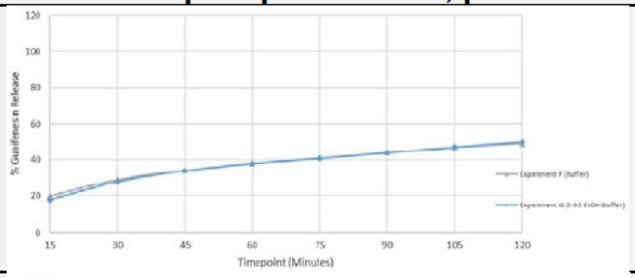
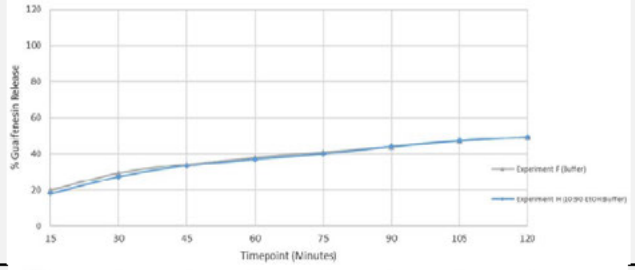
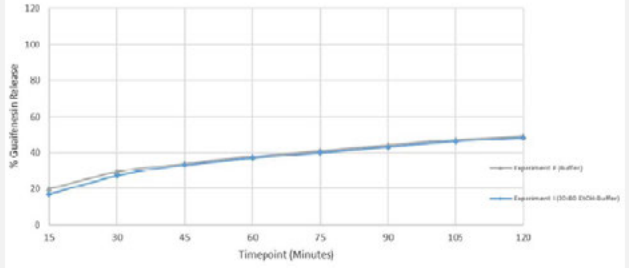
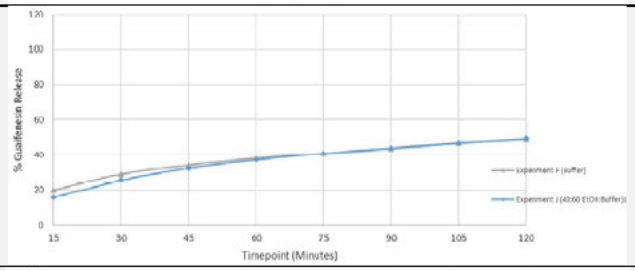
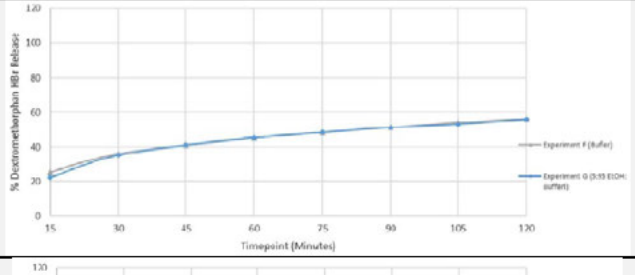
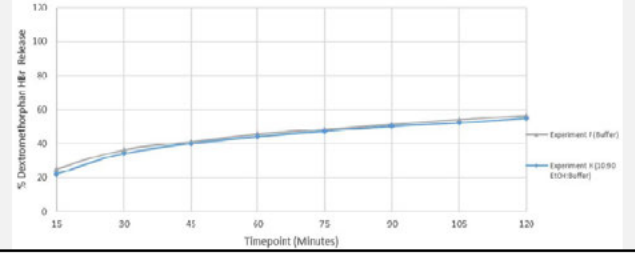
	10%	
	20%	
	40%	
Dextromethorphan HBr	5%	
	10%	
	20%	

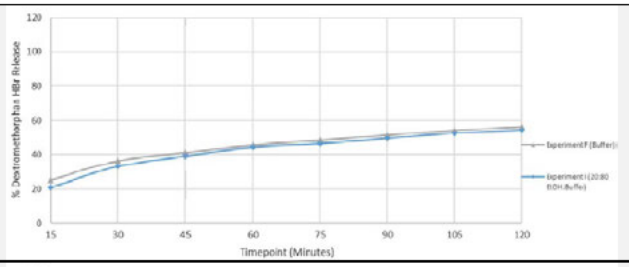
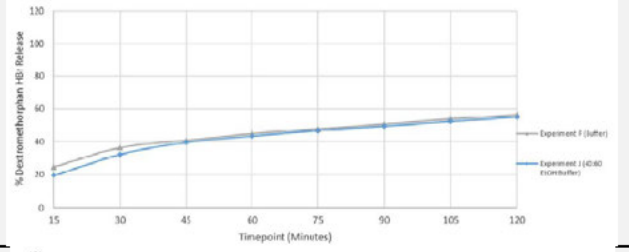
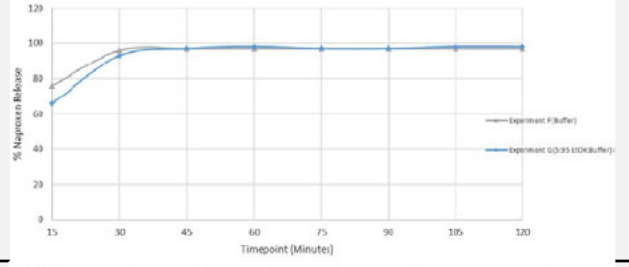
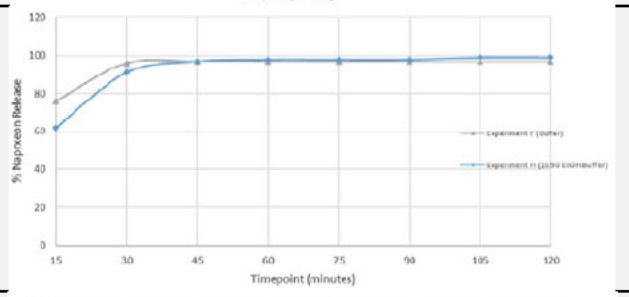
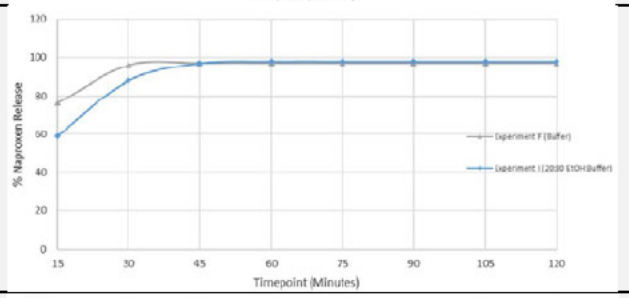
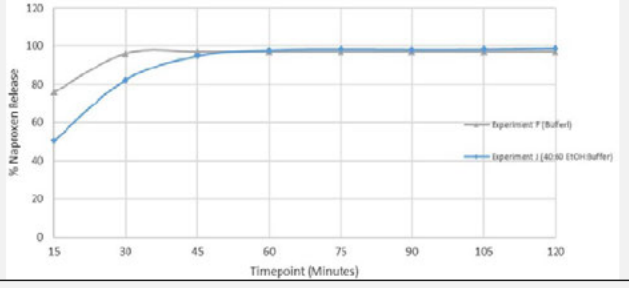
	40%	
Naproxen sodium	5%	
	10%	
	20%	
	40%	

- **50 mM sodium phosphate buffer, pH 6.8, with 5, 10, 20 and 40% ethanol**

The alcohol containing media have no significant impact on dissolution of guaifenesin and dextromethorphan HBr, while naproxen sodium showed significant effect of alcohol in the media on dissolution. (Table 10).

Table 10. Comparative dissolution profiles of guaifenesin, dextromethorphan HBr and naproxen sodium in 50 mM sodium phosphate buffer with alcohol at 5, 10, 20 and 40%

API	50 mM sodium phosphate buffer, pH 6.8	
Guaifenesin	5%	
	10%	
	20%	
	40%	
Dextromethorphan HBr	5%	
	10%	

	20%	
	40%	
Naproxen sodium	5%	
	10%	
	20%	
	40%	

Based on the assessment of the results, the drug release of guaifenesin and dextromethorphan HBr ((b) (4) are not significantly affected in the presence of alcohol, indicating the risk for in vivo alcohol-induced dose dumping (b) (4) is low. The differences in drug release of naproxen are not in the scope of the assessment for alcohol-induced dose dumping (b) (4) .

B.11 EXTENDED RELEASE DOSAGE FORMS –*Extended Release Claim*

Assessment: *Adequate*

The proposed drug product is a FDC tablet containing an immediate release (IR) portion (b) (4) , and an extended-release (ER) layer (b) (4) . From a Biopharmaceutics perspective, the drug product meets the extended release claims made for it as per 21 CFR 320.25(f).

B.12 BRIDGING OF FORMULATIONS

Assessment: *Adequate*

Based on the information provide (response to IR#2 dated 05/06/2024), there is no significant change in the formulation, manufacturing process, manufacturing site or batch size among the pivotal clinical batches, registration and primary stability batches, and the proposed to-be-marketed product (Table 11). Therefore, no additional bridging is warranted.

Table 11 Formulation comparison

Ingredient	Function	Quality Standard	Amount per Unit (mg/Tablet)	% w/w	Clinical Batch & Pivotal Batch 1 Quantity (kg)	Pivotal Batch 2 & 3 Quantity (kg)	Batch # 12224566 Quantity (kg)
							(b) (4)
Guaifenesin	Expectorant	USP					(b) (4)
Dextromethorphan hydrobromide	Antitussive	USP					
Naproxen sodium	Nonsteroidal Anti-inflammatory	USP					
Sodium lauryl sulfate	(b) (4)	NF					
Sodium bicarbonate		USP					
Polyethylene glycol (b) (4)		NF					
Microcrystalline cellulose		NF					
Croscarmellose sodium		NF					
Magnesium stearate		NF					
							(b) (4)
Hypromellose (b) (4)	(b) (4)	USP					(b) (4)
Hydroxyethyl cellulose (b) (4)		NF					
							(b) (4)
FD&C Red No. 40	(b) (4)	Internal					(b) (4)
							(b) (4)
Total weight (Bi-layer Tablets)				(b) (4) (b) (4)			(b) (4)

(b) (4)

B. 13 BIOWAIVER REQUEST

Assessment: *N/A*

The proposed drug product is a single-strength FDC product containing guaifenesin 600 mg, dextromethorphan HBr 30 mg and naproxen sodium 110 mg. No biowaiver request is proposed/needed.

BIOPHARMACEUTICS LIST OF DEFICIENCIES

None

Primary Assessor's Name and Date: Min Sung Suh, Ph.D. 05/10/2024

Secondary Assessor's Name and Date: Kevin Wei, Ph.D. 05/14/2024

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

---

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/

SWAPAN K DE
05/29/2024 08:05:08 PM