CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

217338Orig1s000

OTHER REVIEW(S)

Labeling Review for Mucinex® 12 Hour Cold & Fever Multi-Symptom - Resubmission

SUBMISSION DATES:	September 29, 2023 February 22, 2024 July 7, 2025 October 24, 2025
NDA/SUBMISSION TYPE:	NDA 217338
ACTIVE INGREDIENTS:	Naproxen Sodium 110 mg, dextromethorphan HBr 30 mg, guaifenesin 600 mg
DOSAGE FORM:	Extended-release Tablet
SPONSOR:	RB Health (US) LLC 399 Interpace Parkway, Center 4 Parsippany, NJ 07054 Ebru Unver Kulak Sr Regulatory Manager (973) 631-0773
REVIEWER:	Michelle D. Walker, PhD IDS Pharmacologist
TEAM LEADER:	Robert Bahde, PhD Team Leader
PROJECT MANAGER:	Tam Dinh, PharmD Regulatory Project Manager

Applicant, RB Health, submitted a resubmission to NDA 217338 for an extended-release tablet containing naproxen sodium 110 mg, dextromethorphan HBr 30 mg, and guaifenesin 600 mg. The original proposed proprietary name was [redacted] (b) (4). The Applicant changed the proposed proprietary name to Mucinex 12 Hour Cold & Fever Multi-Symptom with this resubmission. This proposed OTC drug product is directed to be taken two tablets every 12 hours for adults and children 12 years and older.
The proposed indications are:

• helps loosen phlegm (mucus) and thin bronchial secretions to rid the bronchial passageways of bothersome mucus and make coughs 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 the common cold
• temporarily reduces fever

The Applicant referenced in the original submission that it is relying on the safety and efficacy approvals from NDA 020204 (Aleve® 220 mg Tablets) and NDA 021620 (Mucinex® DM Extended-Release Tablets) to support this NDA. The proposed drug facts label (DFL) has been compared to the last approved DFL for both NDAs. The Applicant was issued a complete response (CR) letter due to a clinical deficiency in support of the proposed 12-hour duration of action and dosing regimen of the ER product (July 26, 2024, date of signature).

In this resubmission, to demonstrate clinical efficacy, the Applicant submitted results of their relative bioavailability study to establish a scientific bridge between the proposed product and Aleve-D Sinus & Cold (naproxen 220 mg; pseudoephedrine HCl 120 mg) extended-release (ER) tablet that FDA recommended in the CR letter.

On July 7, 2025, the Applicant resubmitted a complete response for this NDA to address the clinical deficiency identified in the CR letter along with updated labeling for all of the SKUs. On October 24, 2025, the Applicant submitted updated labeling after an information request (IR).

Submitted Draft Labeling	Date submitted
4-count carton HCP sample	9/29/2023 2/22/2024 7/7/2025 10/24/2025
8-count carton	9/29/2023 2/22/2024 7/7/2025 10/24/2025
16-count carton	9/29/2023 2/22/2024 7/7/2025 10/24/2025
32-count carton	9/29/2023 2/22/2024 7/7/2025 10/24/2025
60-count carton	9/29/2023 2/22/2024

Submitted Draft Labeling	Date submitted
	7/7/2025 10/24/2025
4-count blister card	9/29/2023 2/22/2024 7/7/2025
8-count blister card	9/29/2023 2/22/2024 7/7/2025
10-count blister card	9/29/2023 2/22/2024 7/7/2025
4-count peel-back DFL	9/29/2023 2/22/2024 7/7/2025 10/24/2025
8-, 16-, 32-, and 60-count peel-back DFL	9/29/2023 2/22/2024 7/7/2025 10/24/2025
Website mock ups	10/24/2025

I. REVIEWER'S COMMENTS

The submitted labels have been compared to the last approved labeling for NDA 20204 Aleve (S-84) and NDA 21620 Mucinex DM (S-43). Differences between the approved labeling and the proposed labeling are noted below.

A. Outer Container Labeling

1. Principal Display Panel (PDP)

a. A new proprietary name was submitted for review on July 11, 2025, Mucinex 12 Hour Cold & Fever Multi-Symptom.
Reviewer's comment: *DMEPA have concluded that the proposed name is conditionally acceptable (Correspondence to the sponsor signed 9/18/2025).*

b. The proposed proprietary name is placed in the upper center of the PDP. It is centered as seen below:

MUCINEX®
12HR COLD & FEVER
MULTI-SYMPTOM

Reviewer's comment: *This is acceptable, all components of the proprietary name are centered and comparable in size so that the prominence appears equal.*

c. The statement of identity (SOI) is located under the proposed brand name and is bolded and is listed as:

Naproxen Sodium 110 mg (NSAID) » Pain Reliever/Fever Reducer
Dextromethorphan HBr 30 mg » Cough Suppressant
Guaifenesin 600 mg » Expectorant
Extended-Release Tablets

Reviewer's comment: *The SOI is listed correctly in accordance with 21 CFR 201.61 and OTC labeling guidance [1].*

d. A clock image is in the center of the PDP, with "12 Hour" in the middle and with 12 ticks in the image.

e. ***Reviewer's comment:*** *This is acceptable.*

f. The symptoms treated are listed under the clock image and they are as follows:

- ✓ Fever, Headache & Body Pain
- ✓ Cough + Chest Congestion
- ✓ Thins & Loosens Mucus

Reviewer's comment: *These symptom treatment claims are acceptable, they are indicated for use in NDA 20204 Aleve and NDA 21620 Mucinex DM.*

g. A graphic image of the bi-layer extended-release tablet is at the bottom center of the PDP with an "ACTUAL SIZE" descriptor. The graphic image contains a pink layer ((b) (4) and a white layer ((b) (4)).
Reviewer's comment*: This is acceptable.*

h. The net quantity statement "X Extended-Release Tablets" is in the lower left-side corner.
Reviewer's comment*: This is acceptable.*

i. A subdued gray 'M' logo serves as a background design element on the bottom half of the PDP.
Reviewer's comment*: This is acceptable. The gray M background does not conflict with overlayed font and images and is consistent with other approved Mucinex products.*

j. On the 4-count PDP, there is a statement indicating that it is a sample "SAMPLE-NOT TO BE SOLD" in the upper left-side corner.
Reviewer's comment*: This is acceptable.*

k. On the 32-count and 60-count PDPs, there is a red "Value Size" flag at the top of the PDP.
Reviewer's comment*: This is acceptable.*

2. Top Panel

a. There is an actual size image of the bi-layer tablet, identical to the image on the PDP. There is a pink layer ((b) (4)) and a white layer ((b) (4)). The statement "Lasts 12 Hours" follows the "Extended-Release

[1] Draft guidance for industry *Statement of Identity and Strength — Content and Format of Labeling for Human Nonprescription Drug Products* (September 2022)

Layer" label. On the 32- and 60-count top panels, the statement "Bi-Layer Tablet" is under the tablet image.

Reviewer's comment*: This is acceptable. It is consistent with the tablet image and labels for the other Mucinex product lines.*

b. On the 32-count and 60-count labeling, the brand name is also located on the top panel. It is written as follows:

MUCINEX®
12HR COLD & FEVER
MULTI-SYMPTOM

Reviewer's comment: *This is acceptable.*

3. Left-side Panel

a. The following elements are on the left-side panel:

- The barcode (except for the 4-count HCP sample)
- Images for packaging recycling information

- Resource for parents about substance abuse (due to dextromethorphan as an active ingredient) with the corresponding website, www.stopmedicineabuse.org.

- The tamper-evident statement, "Tamper Evident: Do not use if carton is open or if printed seal on blister is broken or missing."

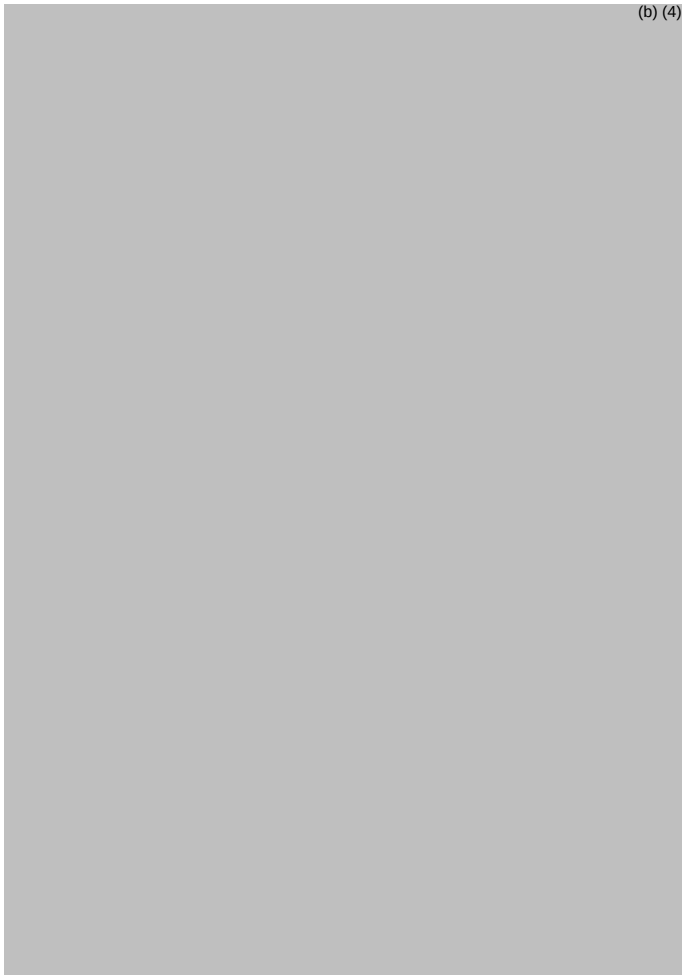
Reviewer's comment: *This content is acceptable. The 4-count HCP sample carton does not have a barcode since it is not for retail sale.*

4. **Right-side Panel**
   a. The following is on the right-side panel:
      - The proposed brand name

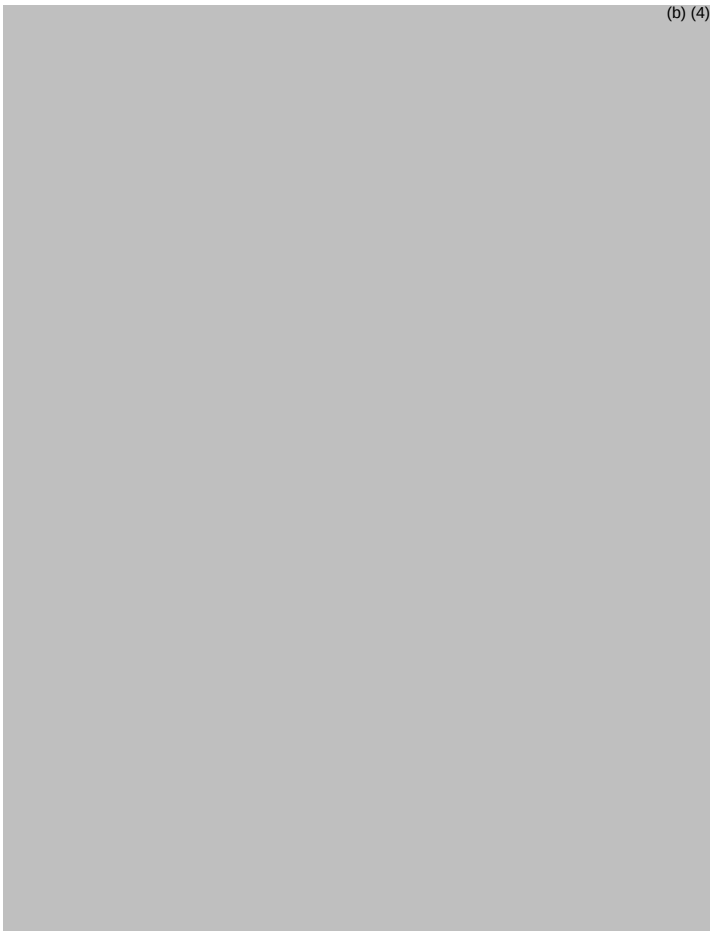
        MUCINEX®
        12HR COLD & FEVER
        MULTI-SYMPTOM
      - A QR code with the instruction "Scan for FAQs and instruction on proper disposal of medicines"
      - The statement "Please visit our website www.mucinex.com"

      Reviewer's comment: *These are acceptable.*

5. **Drug Facts Label (DFL)**
   a. The peel-back DFL for the 4-count carton is 5 panels and the DFL for the other carton sizes is 3 panels.
   b. The content of the DFL is listed below:



1 Page of Draft Labeling has been Withheld in Full as b4 (CCI/ TS) immediately following this page



The differences from the NDA 20204 Aleve (S-84) and NDA 21620 Mucinex DM (S-43) current DFLs are listed below.

- On NDA 20204 Aleve (S-84), the dosage of naproxen sodium is 220 mg per tablet and on the proposed DFL, the strength of naproxen sodium in each proposed tablet is 110 mg.
  Reviewer's comment: *This is acceptable.*
- Under ***Directions****, the direction that "this product can be administered with regard for timing of meals" is on the* NDA 21620 Mucinex DM (S-43) DFL but not included on the proposed DFL.
  Reviewer's comment: *This is acceptable.*

- On the Aleve NDA 20204 DFL, under ***When using this product****,* the direction states "take with food or milk if stomach upset occurs." The same direction is on the proposed DFL.

- The proposed product's dosing, "adults and children 12 years and older: take 2 tablets every 12 hours, not more than 4 tablets in 24 hours," differs from the dosing for the comparator products, Aleve (NDA 020204) and Mucinex DM (NDA 021620), because of the difference in tablet strength. The direction for NDA 21620 Mucinex DM (S-43), is "adults and children 12 years and older: 1 or

2 tablets every 12 hours; not more than 4 tablets in 24 hours." The directions for Aleve (S-84) are:

Adults and children 12 years and older
- take 1 caplet every 8 to 12 hours while symptoms last
- for the first dose you may take 2 caplets within the first hour
- do not exceed 2 caplets in any 8- to 12-hour period
- do not exceed 3 caplets in a 24-hour period

Reviewer's comment: *This is acceptable, DNPD1 medical officers have determined that the 12-hour clinical claims have been sufficiently supported in the resubmission.*

- Under ***Other information*** on the proposed DFL, the sodium content is 26 mg in each tablet and on NDA 20204 Aleve (S-84), the sodium content is 21 mg.
  Reviewer's comment: *This is acceptable. It meets the labeling requirements in 21 CFR 201.64(b).*
- On the proposed DFL, the ***Inactive ingredients*** are croscarmellose sodium, FD&C red no. 40, hydroxyethyl cellulose, hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, sodium bicarbonate, sodium lauryl sulfate.
  Reviewer's comment: *This is acceptable.*

6. Immediate Container (4-, 8-, and 10-count Blister Mats)

a. The brand name is changed to the proposed brand name.

b. One panel contains warnings found on Aleve:
Stomach bleeding warning: This product contains an NSAID, which may cause severe stomach bleeding. The chance is higher if you:
■ are age 60 or older
■ have had stomach ulcers or bleeding problems
■ take a blood thinning (anticoagulant) or steroid drug
■ take other drugs containing prescription or non-prescription NSAIDs (aspirin, ibuprofen, naproxen, or others)
■ have 3 or more alcoholic drinks everyday while using this product
■ take more or for longer time than directed
Reviewer's comment*: This is acceptable, it provides warning information to the user if the carton is discarded.*

c. The Expiration Dating and Lot Number are on the right side of the blister mat "LOT and EXP AREA."
Reviewer's comment*: This is not acceptable.*

d. There is a warning statement, "Keep this warning. Do not detach individual blisters until ready to use." on the same panel as the one containing the NSAID warnings. The panels listing the brand name and SOI, include a warning, "See warnings before use." in addition to the distributor information.
Reviewer's comment*: This is acceptable.*

(b) (4)

7. Website Mockup Pages

a. (b) (4)

b.

c.

d.

e.

f.

Reviewer's comment*: This content is acceptable. It is consistent with the content on the proposed product labeling.*

II. RECOMMENDATIONS

Issue an APPROVAL letter to the sponsor and request that the sponsor submit final printed labeling for the (b) (4) product identical to the labels listed in the table below.

Submitted Draft Labeling	Date submitted
4-count carton HCP sample	10/24/2025
8-count carton	10/24/2025
16-count carton	10/24/2025
32-count carton	10/24/2025
60-count carton	10/24/2025
4-count blister card	7/7/2025
8-count blister card	7/7/2025
10-count blister card	7/7/2025
4-count peel-back DFL	10/24/2025
8-, 16-, 32-, and 60-count peel-back DFL	10/24/2025

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/s/

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M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 12/9/2025

TO: Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)
Office of Neuroscience (ON)
Division of Nonprescription Drugs I (DNPD I)
Office of Nonprescription Drugs (ONPD)

FROM: Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Decline to conduct an on-site inspection**

RE: NDA NON-RESPONSIVE
NDA 217338

The Office of Study Integrity and Surveillance (OSIS) determined that an inspection is not needed for the site listed below. The rationale for this decision is noted below.

Rationale

(b) (4) OSIS conducted an inspection for the site in (b) (4). The inspection was conducted under the following submissions: NDAs NON-RESPONSIVE, NON-RESPONSIVE.

OSIS concluded that data from the reviewed studies were reliable.

Site

Facility Type	Facility Name	Facility Address
Analytical	(b) (4)	

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LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	November 25, 2025
Requesting Office or Division:	Division of Nonprescription Drugs I (DNPDI)
Application Type and Number:	NDA 217338
Product Name, Dosage Form, and Strength	Mucinex 12 HR Cold & Fever Multi-Symptom (naproxen sodium/dextromethorphan HBr/guaifenesin) extended-release tablets, 110 mg/30 mg/600 mg
Product Type:	Multiple Ingredient Product
Rx or OTC:	Over-the-counter (OTC)
Applicant Name:	RB Health US LLC
FDA Received Date:	July 7, 2025 and October 24, 2025
TTT ID #:	2025-15451
DMEPA 2 Safety Evaluator:	Grace P. Jones, PharmD
DMEPA 2 Team Leader:	Tingting Gao, PharmD

1 INTRODUCTION

As part of the approval process for Mucinex 12 HR Cold & Fever Multi-Symptom (naproxen sodium/dextromethorphan HBr/guaifenesin) extended-release tablets, the Division of Nonprescription Drugs I (DNPDI) requested that we review the proposed Mucinex 12 HR Cold & Fever Multi-Symptom container labels and carton labeling for areas of vulnerability that may lead to medication errors.

1.1 REGULATORY HISTORY

RB Health US LLC (RB) previously submitted NDA 217338 on September 29, 2023, which received a Complete Response letter on July 26, 2024 due to a clinical deficiency regarding potential concern for waning or loss of analgesic and antipyretic effects of naproxen before the next dose of the proposed product.[a]

Thus, RB Health US LLC submitted a Class 2 Resubmission on July 7, 2025.[b]

2 MATERIALS CONSIDERED

This section lists the materials considered for our review.

Table 1. Materials Considered for this Review	
Materials Considered	Appendix Section
Relevant Product Information	A
Labels and Labeling	B
Previous DMEPA Reviews	C

3 DISCUSSION

RB is proposing to market a fixed dose combination naproxen sodium/dextromethorphan HBr/guaifenesin extended-release tablet product for OTC marketing as a pain reliever/fever reducer, cough suppressant and expectorant. The proposed product is indicated for adults and children 12 years of age and older and is dosed at two extended-release tablets every 12 hours. RB is relying on safety and efficacy data for NDA 020204 (Aleve) and NDA 021620 (Mucinex DM). RB also conducted a relative bioavailability study to establish a scientific bridge to Aleve-D Sinus & Cold, which addresses the CR letter deficiency and substantiates the 12-hour duration of action and 12-hour dosing interval for the naproxen component.

The proposed Mucinex 12 HR Cold & Fever Multi-Symptom is an addition to the Mucinex product line. See Table 2 for a comparison of RB's Mucinex application products in the Mucinex product line.

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[a] Dinh, T on behalf of Todd, N. Complete Response for NDA 217338. Silver Spring (MD): FDA, CDER, OND, Division of Nonprescription Drugs I (DNPDI) (US); 2024 JUL 26.

[b] Resubmission/Class 2 for NDA 217338 Naproxen sodium/Dextromethorphan HBr. Parsippany (NJ): RB Health US LLC; 2025 JUL 07. Available from: \\CDSESUB1\EVSPROD\nda217338\0023\m1\us\12-cov-let\cover.pdf.

Table 2. Comparison of Application Mucinex Product Line (RB Health)				
	Mucinex 12 HR Cold & Fever Multi-Symptom [proposed][c]	Mucinex[d]	Mucinex DM[e]	Mucinex D[f]
Application #	NDA 217338	NDA 021282	NDA 021620	NDA 021585
Active Ingredient(s)	Naproxen sodium Dextromethorphan HBr Guaifenesin	Guaifenesin	Dextromethorphan HBr Guaifenesin	Guaifenesin Pseudoephedrine HCl
Strength	110 mg/30 mg/600 mg	600 mg 1200 mg	30 mg/600 mg 60 mg/1200 mg	600 mg/60 mg 1200 mg/120 mg
Dosage Form	Extended-release tablet			
Approval Date	N/A	07/12/2002	04/29/2004	06/22/2004
Carton Labeling Principal Display Panel (PDP) Image	(b) (4)	(b) (4)		

Compared with the currently marketed Mucinex, Mucinex DM, and Mucinex D products, the proposed Mucinex 12 HR Cold & Fever Multi-Symptom PDP uses a different color scheme featuring light grey and white background colors, which helps distinguish it from the existing products. The similarities on the PDP include the 12-hour clock-like graphic image, the product specific symptom claims, and graphic image of the extended-release tablet. The modifier "12HR" in the proprietary name Mucinex 12HR Cold & Fever Multi-Symptom is presented in red font color, which provides differentiation between the existing products and does not detract from readability of the entire proprietary name.

The proposed carton labeling contains the Drug Facts label (DFL) on a 'peel and reveal' design, presenting the DFL across multiple pages ('ply'). The statement "PEEL CORNER FOR COMPLETE

[c] Clinical/Response To Information Request; Labeling/Container-Carton Draft for NDA 217338. Parsippany (NJ): RB Health US LLC; 2025 OCT 24.

[d] Mucinex NDA 021282/S-055. Drugs@FDA. U.S. Food and Drug Administration. AUG 2024. [cited 2025 NOV 12]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/021282Orig1s055lbl.pdf.

[e] Mucinex DM NDA 021620/S-045. Drugs@FDA. U.S. Food and Drug Administration. AUG 2024. [cited 2025 NOV 12]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/021620Orig1s045lbl.pdf.

[f] Mucinex D NDA 021585/S-038. Drugs@FDA. U.S. Food and Drug Administration. JUL 2024. [cited 2025 NOV 12]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/021585Orig1s038lbl.pdf.

DRUG FACTS" appears in all uppercase bold type at the bottom left corner to indicate that additional information is available on the subsequent pages ('ply').

The proposed blister card container labels include a blister cell containing warnings information, and each blister cell holds two extended-release tablets, corresponding to the two-tablet dose. The proposed 4-count and 8-count blister card container labels include an additional blister cell that displays only the proprietary name and the statement of identity (SOI) without the two-tablet dose.

RB included a graphic image of an extended-release tablet on the PDP of the proposed carton labeling, accompanied by the statement "ACTUAL SIZE" below the image. To ensure accuracy, the following recommendation was sent in an Information Request (IR) to RB: *Ensure that the graphic image of the proposed extended-release tablet presented on the carton labeling represents a true depiction of the actual tablet, reflecting the tablet size, shape, color, and imprint*. Additionally, although the recommended dosage requires two tablets, an image depicting two extended-release tablets on the PDP was not needed because each blister cell contains a two-tablet dose. The review team also included a recommendation in this IR to: *Increase the type size of the term "Multi-Symptom" so that the entire proprietary name is equal in prominence*. RB responded on October 24, 2025, and implemented these recommendations.[g]

4 CONCLUSION

Our evaluation of the proposed Mucinex 12 HR Cold & Fever Multi-Symptom container labels and carton labeling did not identify areas of vulnerability that may lead to medication errors. We have no further recommendations at this time.

[g] Clinical/Response to Information Request; Labeling/Container-Carton Draft for NDA 217338. Parsippany (NJ): RB Health US LLC; 2025 OCT 24. Available from: \\CDSESUB1\EVSPROD\nda217338\0030\m1\us\111-info-amend\resp-ir.pdf.

APPENDICES: MATERIALS CONSIDERED FOR THIS REVIEW

APPENDIX A. RELEVANT PRODUCT INFORMATION

Table 3 presents relevant product information for Mucinex 12 HR Cold & Fever Multi-Symptom received on July 7, 2025 from RB Health US LLC.

Table 3. Relevant Product Information for Mucinex 12 HR Cold & Fever Multi-Symptom	
Initial Approval Date	N/A
Active Ingredient	naproxen sodium/dextromethorphan HBr/guaifenesin
Indication	Drug Facts label (DFL) *Uses*: ***Uses*** ■ helps loosen phlegm (mucus) and thin bronchial secretions to rid the bronchial passageways of bothersome mucus and make coughs 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 the common cold ■ temporarily reduces fever
Dosage Form	extended-release tablets
Strength	110 mg/30 mg/600 mg
Route of Administration	oral
Dose and Frequency	DFL *Directions*: ***Directions*** ■ do not crush, chew, or break extended-release tablet ■ **do not take more than directed** ■ take each dose with a full glass of water ■ adults and children 12 years and older: take 2 extended-release tablets every 12 hours; not more than 4 extended-release tablets in 24 hours ■ children under 12 years of age: do not use
How Supplied	o 4-count blister card o 10-count blister card o 4-count carton (containing one 4-count blister card) – HCP sample o 8-count, 16-count, and 32-count cartons containing one, two, and three 8-count blister cards, respectively o 60-count carton containing six 10-count blister cards
Storage	store at 20-25°C (68-77°F). Avoid excessive heat above 40°C (104°F)

APPENDIX B. LABELS AND LABELING

B.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[h] along with postmarket medication error data, we reviewed the following Mucinex 12 HR Cold & Fever Multi-Symptom labels and labeling submitted by RB Health US LLC.

- Container label(s) received on July 7, 2025
- Carton labeling received on October 24, 2025

B.2 Container Label(s) and Carton Labeling Images

Container Label(s):

4-Count Blister Card – enlarged image:

[h] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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APPENDIX C. PREVIOUS DMEPA REVIEWS

On November 10, 2025, we searched for previous DMEPA reviews relevant to this current review using the term Mucinex. Our search identified several previous reviews, and we considered our previous recommendations to see if they are applicable for this current review.

Table 4. List of Previous DMEPA Reviews for Mucinex

Application #	Product name	Strength	Status	Previous DMEPA Reviews
NDA 021282	Mucinex (guaifenesin) tablets	600 mg 1200 mg	Approved on 7/12/2002	2012-2106 2024-9482
NDA 021585	Mucinex D (Guaifenesin and Pseudoephedrine Hydrochloride)	600 mg/60 mg 1200 mg/120 mg	Approved on 6/22/2004	2024-8141
NDA 021620	Mucinex DM (Dextromethorphan Hydrobromide and Guaifenesin)	30 mg/600 mg 60 mg/1200 mg	Approved on 4/29/2004	2012-2106 2024-8713
NDA 217338	Mucinex 12 HR Cold & Fever Multi-Symptom (naproxen sodium/dextromethorphan HBr/guaifenesin) extended-release tablets	110 mg/30 mg/600 mg	Subject of this review	2025-15451

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/s/

GRACE JONES
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M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 8/26/2025

TO: Division of Nonprescription Drugs I (DNPD I)
Office of Nonprescription Drugs (ONPD)

FROM: Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Decline to conduct an on-site inspection**

RE: NDA 217338

The Office of Study Integrity and Surveillance (OSIS) determined that an inspection is not needed for the site listed below. The rationale for this decision is noted below.

Rationale

The Office of Inspections and Investigations (OII) conducted an inspection of the site in August 2024. The inspection was conducted under the following submission: NDA non-responsive .

The following items were discussed with the site:

(b) (4)

After review of the discussion items, OSIS concluded that the findings did not impact data reliability or human subject protection.

Site

Facility Type	Facility Name	Facility Address
Clinical	Syneos Health, Inc.	1951 Northwest 7th Avenue, Suite 450, Miami, FL

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JAMES J LUMALCURI
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Labeling Review for Mucinex® 12 Hour Cold & Fever Multi-Symptom

SUBMISSION DATES:	September 29, 2023 February 22, 2024
NDA/SUBMISSION TYPE:	NDA 217338
ACTIVE INGREDIENTS:	Naproxen Sodium 110 mg, dextromethorphan HBr 30 mg, guaifenesin 600 mg
DOSAGE FORM:	Extended-release Tablet
SPONSOR:	RB Health (US) LLC 399 Interpace Parkway, Center 4 Parsippany, NJ 07054 Ebru Unver Kulak Sr Regulatory Manager (973) 404-2807
REVIEWER:	Michelle D. Walker, PhD IDS Pharmacologist
TEAM LEADER:	Steven Adah, PhD Team Leader (Acting)
PROJECT MANAGER:	Tam Dinh, PharmD Regulatory Project Manager

The sponsor submitted a NDA for an extended-release tablet containing naproxen Sodium 110 mg, dextromethorphan HBr 30 mg, and guaifenesin 600 mg. The original proposed proprietary name was [redacted] (b) (4). This proposed OTC drug product is directed to be taken two tablets every 12 hours for adults and children 12 years and older.

The proposed indications are as follows:

- helps loosen phlegm (mucus) and thin bronchial secretions to rid the bronchial passageways of bothersome mucus and make coughs 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 the common cold

• temporarily reduce fever

The sponsor referenced in the original submission that it is relying on the safety and efficacy approvals from NDA 020204 (Aleve® 220 mg Tablets) and NDA 021620 (Mucinex® DM Extended-Release Tablets) to support this NDA. The proposed drug fact label (DFL) has been compared to the last approved DFL for both NDAs. The sponsor will be issued a complete response due to outstanding issues concerning providing data that symptoms treated by naproxen will be treated for 12 hours.

Submitted Draft Labeling	Date submitted
4-count carton HCP sample	9/29/2023 & 2/22/2024
8-count carton	9/29/2023 & 2/22/2024
16-count carton	9/29/2023 & 2/22/2024
32-count carton	9/29/2023 & 2/22/2024
60-count carton	9/29/2023 & 2/22/2024
4-count blister card	9/29/2023 & 2/22/2024
8-count blister card	9/29/2023 & 2/22/2024
10-count blister card	9/29/2023 & 2/22/2024
4-count peel-back DFL	9/29/2023 & 2/22/2024
8-, 16-, 32-, and 60-count peel-back DFL	9/29/2023 & 2/22/2024

I. REVIEWER'S COMMENTS

The submitted labels have been compared to the last approved labeling for NDA 20204 Aleve (S-84) and NDA 21620 Mucinex DM (S-43). Differences between the approved labeling and the proposed labeling are noted below.

A. Outer Container Labeling

1. Principal Display Panel (PDP)

A new proprietary name is being proposed, Mucinex 12 Hour Cold & Fever Multi-Symptom, it was submitted for review on October 6, 2023. The NDC number is in upper left corner of the PDP.

a. ***Reviewer's comment:*** *In the original submission, the sponsor submitted a different proposed proprietary name,* (b) (4) *. DNPDI medical officers reviewed the currently approved indications for the three active ingredients,* (b) (4) *DMEPA held a teleconference with the sponsor on December 6, 2023, to discuss preliminary findings for the proposed proprietary name. It was identified that the listed drug products and the proposed product* (b) (4) *. On December 11, 2023, the sponsor withdrew the proposed proprietary name,* (b) (4) *. The sponsor then submitted a new proposed proprietary name, Mucinex 12 HR Cold & Fever Multi-Symptom, for review on December 19, 2023 under NDA 217338.The proposed product's 12-hour dosing interval is a review issue at the time of this review, due to the dose of naproxen directed for use for this product is not indicated to be efficacious for a 12 hour period. DMEPA has determined that the proposed proprietary name is conditionally acceptable (March 8, 2024 review).*The proposed proprietary name is placed in the upper center of the PDP. It is centered as seen below:

MUCINEX®
12HR COLD & FEVER
MULTI-SYMPTOM

"Multi-Symptom" is written in a smaller font.

Reviewer's comment: *On the currently approved Mucinex PDPs, the brand name and statement of identity (SOI) are encased in the box with any descriptors under the box. Per 21 CFR 201.61the brand name should be displayed in the same manner with the SOI. DNPDI can recommend any changes to the centering of the tradename once the proprietary name is approved.*

b. The SOI is under the proposed brand name and is listed as:

Naproxen Sodium 110 mg (NSAID) » Pain Reliever/Fever Reducer
Dextromethorphan HBr 30 mg » Cough Suppressant
Guaifenesin 600 mg » Expectorant

Reviewer's comment: *On the currently approved Mucinex DM (NDA 21620) PDP, "extended-release tablets" are part of the SOI. The same should be done for the SOI on this proposed labeling. The rest of the SOI is listed correctly, in line with how the active ingredients are listed in the SOI for NDA 20204 Aleve and NDA 21620 Mucinex DM. Per 201.61(c) the SOI also needs to be bolded.*

c. A clock image is in the center of the PDP, with "12 Hour" in the middle and with (b) (4) ticks in the image.
Reviewer's comment: *It is still under review as whether the proposed product will approved for the 12 hour claim, so the clock image containing "12 Hour" cannot be approved at this point, If the clock image will remain, the number of ticks in the image will have to be* (b) (4) *12 ticks, so that's clear to consumers that the image is supposed to indicate a clock.*

d. The symptoms treated are listed under the clock image and they are as follows:
   - ✓ Fever, Headache & Body Pain
   - ✓ Cough + Chest Congestion
   - ✓ Thins & Loosens Mucus

Reviewer's comment: *These symptom treatment claims are acceptable, they indicated for use for NDA 20204 Aleve and NDA 21620 Mucinex DM.*

e. An image of the bi-layer extended release tablet is at the bottom center of the PDP.
Reviewer's comment*: An "actual size" descriptor should be added next the bi-layer tablet,* (b) (4) *. Additionally, the sponsor should ensure that the graphic image of the extended-release tablet presented on the carton labeling represents a true depiction of the actual tablet including the true tablet size, shape, color, and imprint of the actual tablet.*

f. The net quantity statement "X Extended-Release Tablets" is in the lower left-side corner.
Reviewer's comment*: This is acceptable.*

g. A gray "M" image is covering the bottom half of PDP, in the background.

h. ***Reviewer's comment****: This is acceptable, The gray M background does not conflict with overlayed font and images and is consistent with other approved Mucinex products.*On the 4-count PDP, there is statement indicating that it is a sample "SAMPLE- NOT TO BE SOLD" in the upper left-side corner.
Reviewer's comment*: This is acceptable.*

i. On the 32-count PDP, there is a red "Value Size" flag at the top of the PDP.
Reviewer's comment*: This is acceptable. The sponsor will be asked why the 60-count carton labeling does not also include a value size flag.*

2. Top Panel

a. There is an actual size image of the bi-layer tablet, identical with the image on the PDP. There is a pink layer ((b) (4)) and a white layer ((b) (4)). Each layer of the tablet image is labeled (b) (4) (b) (4)
Reviewer's comment*: This is acceptable, it is in line with tablet image and labels for the other Mucinex product lines' labeling.*

b. On the 32-count and 60-count labeling, the brand name is included on the top panel. It is written as follows:

(b) (4)

Reviewer's comment: *Inclusion of the proposed brand name with* (b) (4) *is not acceptable. FDA recommended that* (b) (4) *be removed from the SOI* (b) (4)*).*

3. **Left-side Panel**
   a. The following is on the left-side panel:
      - The barcode (with the exception of the 4-count HCP sample)
      - Images for packaging recycling information

      - Resource for parents about substance abuse (due to dextromethorphan as an active ingredient) with the corresponding website, www.stopmedicineabuse.org.

      - The tamper-evident statement, "Tamper Evident: Do not use if carton is open or if printed seal on blister is broken or missing."

Reviewer's comment: *This content is acceptable. The 4-count HCP sample carton does not have a barcode since it is not for retail sale.*

4. **Right-side Panel**
   a. The following is on the right-side panel:
      - The proposed brand name

(b) (4)

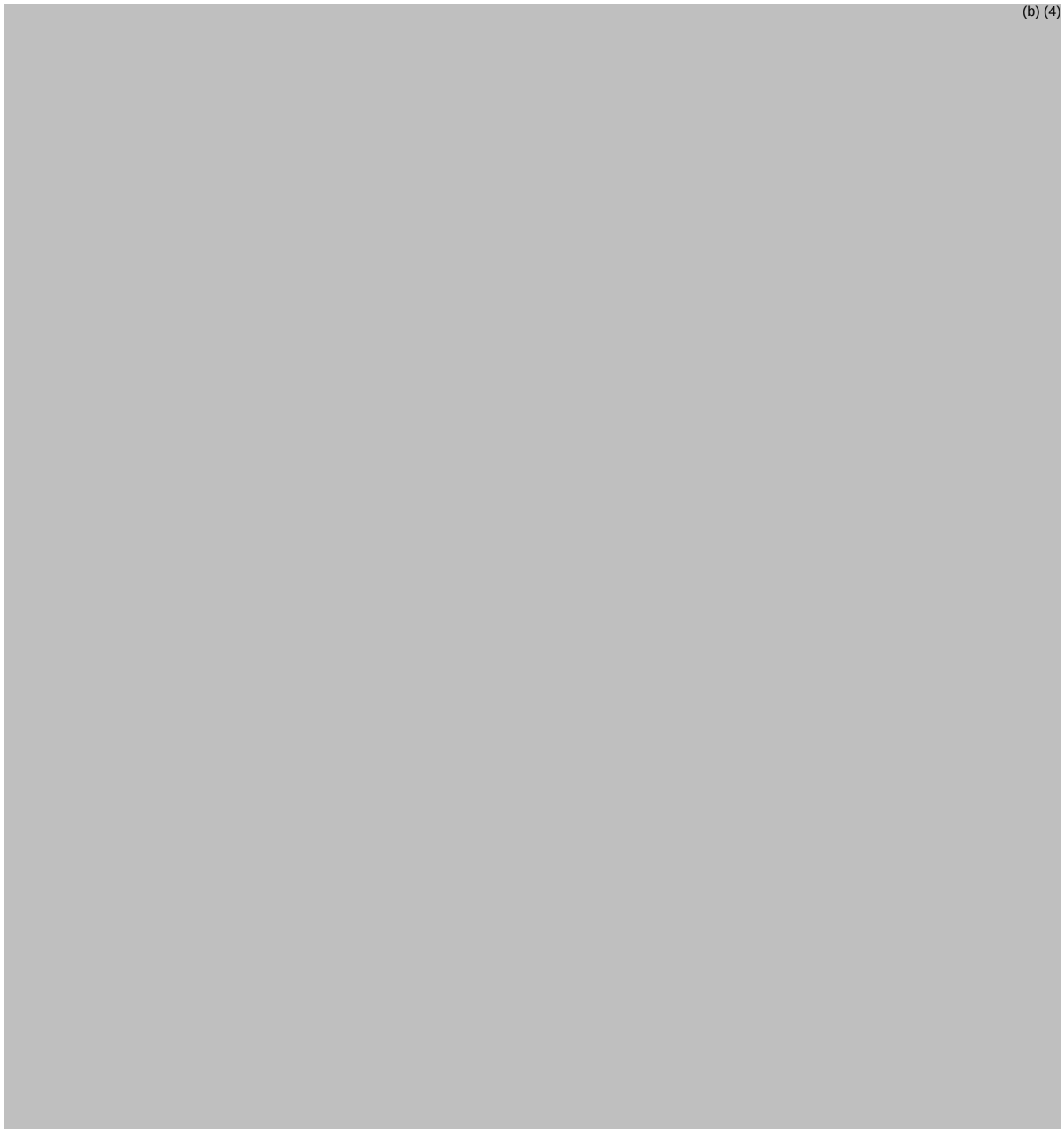
(b) (4)

- The claims (b) (4)
- A QR code with the instruction "Scan for FAQs and instruction on proper disposal of medicines"
- The statement "Please visit our website www.mucinex.com"

Reviewer's comment: *The 12 hour claim is still under review, so the content cannot be approved at this time. Since this is not an approved product and is not currently on www.mucinex.com, the sponsor will have to provide mockups of the content for the proposed product.*

5. **Drug Facts Label (DFL)**
   a. The peel-back DFL for the 4-count carton is 5 panels and the DFL for the other carton sizes is 3 panels.
   b. The content of the DFL is listed below:

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



The differences from the NDA 20204 Aleve (S-84) and NDA 21620 Mucinex DM (S-43) current DFLs are listed below:

- On NDA 21620 Mucinex DM (S-43), the dosage form nomenclature is listed as "Active ingredient (in each extended-release tablet)." On the proposed DFL it is listed as "Active ingredient (in each tablet)."
  Reviewer's comment: *The dosage form nomenclature should be changed to mirror that used on the current* NDA 21620 Mucinex DM (S-43) DFL.
- On NDA 20204 Aleve (S-84), the dosage of naproxen sodium is 220 mg per tablet and on the proposed DFL, the dosage of naproxen sodium is 110 mg per tablet.
  Reviewer's comment: *This acceptable.*

- On NDA 21620 Mucinex DM (S-43), Under the Directions heading, the dosage form nomenclature is "(b) (4)". On the proposed DFL it is listed as "tablets".
  Reviewer's comment: *The dosage form nomenclature should be changed to mirror that used on the current* NDA 21620 Mucinex DM (S-43) DFL.
- Under ***Directions****, the direction that "this product can be administered with regard for timing of meals" is on the* NDA 21620 Mucinex DM (S-43) DFL but not included on the proposed DFL.
  Reviewer's comment: *This is acceptable. On the Aleve NDA 20204 DFL, under* ***When using this product****, the direction states "take with food or milk if stomach upset occurs." The same direction is on the proposed DFL.*

- The direction for dosing is different for this proposed product in that adults and children 12 years and older: take 2 tablets every 12 hours, not more than 4 tablets in 24 hours." On NDA 21620 Mucinex DM (S-43) DFL, the direction is "adults and children 12 years and older: 1 or 2 tablets every 12 hours; not more than 4 tablets in 24 hours." On the Aleve (S-84) DFL, the directions for dosing are Adults and children 12 years and older
  - take 1 caplet every 8 to 12 hours while symptoms last
  - for the first dose you may take 2 caplets within the first hour
  - do not exceed 2 caplets in any 8- to 12-hour period
  - do not exceed 3 caplets in a 24-hour period

  Reviewer's comment: *The efficacy claim of 12 hours of 220 mg of naproxen sodium is still under review by DNPDI medical officers.*
- Under ***Other information*** on the proposed DFL, the sodium content is 26 mg in each tablet and on NDA 20204 Aleve (S-84), the sodium content is 21 mg.
  Reviewer's comment: This is acceptable, if CMC confirms that it is accurate.
- On the proposed DFL, the ***Inactive ingredients*** are croscarmellose sodium, FD&C red no. 40, hydroxyethyl cellulose, hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, sodium bicarbonate, sodium lauryl sulfate.
  Reviewer's comment:. CMC will determine whether the final formulation is approvable after the CR issues are resolved.

6. Immediate Container (4-, 8-, and 10-count Blister Mats)

a. The brand name is changed to the proposed brand name.
b. One panel contains warnings found on Aleve:
   Stomach bleeding warning: This product contains an NSAID, which may cause severe stomach bleeding. The chance is higher if you:
   ■ are age 60 or older
   ■ have had stomach ulcers or bleeding problems
   ■ take a blood thinning (anticoagulant) or steroid drug

■ take other drugs containing prescription or non-prescription NSAIDs (aspirin, ibuprofen, naproxen, or others)
■ have 3 or more alcoholic drinks every day while using this product
■ take more or for longer time than directed

Reviewer's comment*: This is acceptable, it provides warning information to the user if the carton is discarded.*

c. (b) (4) the lot number and expiration date is on the right side of the blister mat" LOT and EXP (b) (4)

Reviewer's comment*: This is not acceptable. After the CR issues are resolved, an information request will be sent to the sponsor concerning this statement.*

d. There is a warning statement "Keep this warning. Do not detach individual blisters until ready to use." on the same panel as the one containing the NSAID warnings. The panels listing the brand name and SOI, include a warning, "See warnings before use." in addition to the distributor information.

Reviewer's comment*: This is acceptable.*

(b) (4)

II. RECOMMENDATIONS

Since this supplement will be issued a complete response, this labeling supplement is not recommended for approval. The labeling submitted in this supplement appears to be complete and no further information requests for labeling are required at this point.

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/s/

MICHELLE D WALKER
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STEVEN A ADAH
05/30/2024 01:15:29 PM
While there are outstanding issues with the labeling, they do not need to be addressed at this time given the pending CR issues for this NDA

FOOD AND DRUG ADMINISTRATION
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Consult Response

TO: Tam Dinh, Pharm D
Regulatory Project Manager
Division of Nonprescription Drugs 1 (DNPD1)
OND, CDER

FROM: Timothy Jiang, MD, PhD
Medical Officer
Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)

THROUGH: Nancy Clark Dickinson, Pharm D
Clinical Team Leader
DAAP

Alla Bazini, MD
Associate Director for Therapeutics Review, Anesthesiology
DAAP

Rigoberto Roca, MD
Division Director
DAAP

SUBJECT: Consult Response, re NDA 217338, guaifenesin, dextromethorphan hydrobromide, and naproxen sodium extended-release tablets

SOURCE DOCUMENT: Consult Request, Submissions to NDA 217338 and Biopharmaceutical Review for NDA 020204

DATE of REQUEST: December 6, 2023

DATE of RESPONSE: February 21, 2024 (draft emailed); May 20, 2024

Executive Summary

On September 29, 2023, the Division of Nonprescription Drugs 1 (DNPD 1) received an NDA (NDA 217338) for (b) (4). This is a fixed dose combination (FDC) product of guaifenesin, dextromethorphan hydrobromide, and naproxen sodium extended-release tablet. DNDP 1 consulted DAAP's clinical team for advice regarding whether a plasma concentration of 15,000 ng/mL of naproxen sodium 220 mg equates to a clinically meaningful benefit for this FDC product. DNDP 1 also requested advice about the proposed every 12 hours dosing interval. The proposed product indication is for cough and cold symptoms, including fever or aches.

DAAP's clinical team evaluated the Applicant's NDA 217338 submission and concludes that, although the Applicant cited the summary reviews from NDA 020204 approval package to support their assertion regarding their product's efficacy, they did not provide adequate data or justification to support their assertion that a human plasma concentration of 15,000 ng/mL of naproxen sodium will provide a clinically meaningful analgesic benefit. This is discussed further below in this document.

We also conclude that the Applicant's original NDA submission does not support every 12 hours dosing interval for the naproxen sodium component of the FDC because, based on the reference product, Aleve tablets NDA 020204, some patients may need re-dosing between 8 and 12 hours to maintain analgesic or the anti-pyretic effect of naproxen sodium 220 mg tablets. During the review cycle, on April 12, 2024, the Applicant responded to a DNDP 1 information request with information that the NDA 217338 application was additionally referencing Aleve-D Sinus & Cold, NDA 021076, which is labeled with a dosing interval of every 12 hours. However, the Applicant did not provide an adequate scientific bridge from their proposed FDC to NDA 021076. Therefore, data from NDA 021076 every 12-hour dosing cannot be utilized to support the proposed dosing interval for the proposed FDC product.

Background

On September 29, 2023, RB Health submitted NDA 217338 to the DNDP 1 for a fixed dose combination of guaifenesin 600 mg, dextromethorphan hydrobromide 30 mg, and naproxen sodium 110 mg extended-release tablet ((b) (4)). The application utilizes the 505(b)(2) regulatory pathway referencing NDA 021620 Mucinex DM and NDA 020204 Aleve tablets.

On December 6, 2023, DNDP 1 consulted DAAP to opine on the Sponsor's submission that stated that a plasma concentration of 15,000 ng/mL of naproxen sodium 220 mg (Nap) equates to a clinically meaningful benefit for their FDC product. After the Joint Assessment Meeting #3 for NDA 217338 on January 31, 2024, DNDP 1 requested that DAAP also provide an assessment of the proposed dosing interval for the FDC.

The Applicant did not conduct clinical studies to evaluate efficacy of the proposed FDC for NDA 217338. From Nap perspective, the Applicant conducted Study RB5-US-1505, a pharmacokinetic (PK) study in healthy volunteers, to demonstrate bioequivalence as the scientific bridge between its proposed FDC product to Aleve tablet that is dosed Q8-12 hours (Study RB5-US-1505 does not have an arm of the second intended reference, Aleve-D Sinus &

Cold, that is dosed every 12 hours. Therefore, there is no direct scientific bridge between the proposed FDC product to Aleve-D Sinus & Cold). Applicant's collected PK data in both the fasted and fed conditions. These data indicate that the Nap plasma concentrations of the study drug (two tablets of Naproxen Sodium 110 mg, Dextromethorphan HBr 30 mg, and Guaifenesin 600 mg) for both conditions and of the reference (one Aleve tablet, 220 mg, co-administered with two tablets of Mucinex DM) all follow the same curve over time and remain above the plasma concentration level of 15,000 ng/mL for 11 to 12 hours. The Applicant further asserts that data from NDA 20204 Aleve "revealed that a concentration of 15,000 ng/mL of naproxen (at a 220 mg dose) was identified as the effective level for achieving a meaningful reduction in pain."

Discussion of Plasma Concentration

The Applicant's Clinical Summary of Efficacy in Module 2.7.3 of NDA 217338 states, "The data from the original Aleve approval package (NDA 020204) revealed that a concentration of 15,000 ng/mL of naproxen (at a 220mg dose) was identified as the effective level for achieving a meaningful reduction in pain." The Applicant's PK data from Study RB5-US-1505 demonstrated that their Nap 220 mg single dose maintained a plasma concentration above 15,000 ng/mL (15 µg/mL) between 1 to 11 or 12 hours post dose.

It appears that the Applicant is utilizing summary reviews from NDA 020204 approval package to support their assertion regarding their product's efficacy. The original discussion of the 15 µg/mL concentration level for naproxen was based on Study LAB693, conducted in support of NDA 020204, Aleve 220 mg tablets (approved in 1994). Study LAB693 was a placebo-controlled PK and pharmacodynamic (PD) molar extraction study, entitled, *The relationship between the concentration of naproxen in plasma to analgesic efficacy in the treatment of dental pain secondary to surgery for dental impaction*. According to the Biopharmaceutics Review[1] of NDA 020204, dated January 6, 1994, Study LAB693 evaluated naproxen (b) (4) tablet instead of the final to-be-marketed dosage form (i.e., Nap 220 mg tablet). Pain scores were recorded at various timepoints up to 8 hours post dose. The study did not reveal a separation of pain intensity difference (PID) between the placebo and study drug nor PK dose proportionality until 2 hours. The review of LAB693 included an observation that to achieve a PID reduction of 1 unit on the 4-point pain scale, the plasma concentration of naproxen must exceed ~15 µg/ml or greater. The reviewer also noted that, "Whether or not free drug concentration rather than total drug concentration is responsible for the dose-response was unknown." In addition to the fact that Study LAB693 did not evaluate the to-be-marketed formulation of the product, the biopharmaceutical reviewer noted many "flaws" in methodology of the study, which further puts into question the interpretability of the study results.

DAAP's current interpretation of Study LAB 693 is that the PK/PD and dose-finding study (i.e., naproxen 50 to 500 mg) was used for guiding the formulation development under NDA 020204, not to support the efficacy threshold, 15 µg/mL, of the study drug. This study was not designed to provide substantial evidence of efficacy. In addition, according to the approval package for

[1] NDA 020204 Biopharmaceutics Review by E. Dennis Bashaw, pages 27 to 35 of the NDA 020204 action package dated and signed January 6, 1994; (pages 25 to 33 of the scanned action package)

NDA 020204, to support the indication, a total of 34 studies including seven clinical studies evaluating dental pain were conducted.

In summary, DAAP has identified the following concerns regarding the Applicant's assertion that the plasma concentration of 15,000 ng/mL of naproxen equates to a reaching a clinically meaningful analgesic benefit.

1. The Applicant may not have right of reference to Bayer's data from NDA 020204 summary reviews. We defer to DNDP 1 on this point.
2. Study LAB693 (NDA 020204) was designed as a dose-finding study to guide formulation development and not to provide substantial evidence of efficacy of naproxen sodium 220 mg tablets.
    a. The substantial evidence of efficacy of Nap in NDA 020204 was based on data from a total of 34 studies reviewed under the application.
    b. Study LAB693 evaluated multiple doses of naproxen (i.e., 50 to 500 mg). Instead of naproxen sodium 220 mg, the study evaluated free acid naproxen 187.5 mg.
    c. The biopharmaceutical review from NDA 020204 identified "flaws" in the study's methodology. The Applicant's interpretation of the 15 µg/mL threshold from cross-study comparison between LAB693, conducted in the 1990's, and the Applicant's bioequivalence studies (both demonstrating plasma concentrations at or greater than 15 ug/mL) may be affected by changes in methodology such as different subject ages, sex, or body mass index, and different bioanalytical methods.
3. There is not adequate information to support the Applicant's assertion that a 15 µg/mL plasma concentration is the efficacious threshold for Nap 220 mg in the Applicant's FDC product.

Discussion of Dosing Interval

For NDA 217338, the proposed dose and dosing interval for the FDC product is two tablets every 12 hours. Two tablets of the FDC equates to Nap 220 mg. The Applicant was advised during their Pre-NDA meeting to provide data/information to support the proposed fixed 12-hour dosing interval for the Nap component.

The Applicant's rationale for proposing a dosing interval of every 12 hours from the Summary of Clinical Efficacy in Module 2.7.3 of NDA 217338 is summarized below.

1. As described in the Discussion of Plasma Concentration Section above, the Applicant for NDA 217338 stated that Nap plasma concentrations from its proposed product in both fasted and fed conditions achieved the 15,000 ng/mL level for a duration of 11 to 12 hours. "These findings indicate that the combinations [test vs. reference (Aleve 220 mg tablets) drugs] and dosing conditions [fasted and fed] evaluated in the study could potentially offer sustained analgesia effects."

2. The Nap 110 mg component in the Applicant's proposed FDC and the approved Aleve-D Sinus & Cold (naproxen sodium 220 mg, pseudoephedrine hydrochloride 120 mg extended-release tablet), NDA 021076, approved on November 29, 1999, have the same dosing interval of every 12 hours. The Applicant noted that the recommended dosage for

Aleve-D Sinus & Cold was one caplet every 12 hours. The Applicant hypothesized that because NDA 021076, Aleve-D Sinus & Cold, relied upon the safety and effectiveness of NDA 020204, Aleve 220 mg tablets and the Applicant's FDC relies on NDA 020204, the approved dosing interval of every 12 hour for NDA 021076 would be applicable to the Nap component proposed in the current NDA 217338.

3. Lastly, the Applicant's Naproxen Sodium Clinical Efficacy Section in Module 2.7.3.3.4 of the NDA 217338 submission, describes several published studies of naproxen sodium 250 mg or 440 mg administered every 12 hours which demonstrated "significantly better total pain relief" compared to the comparator treatments.

We do not agree with the Applicant's rationale in their original NDA submission dated September 29, 2023, for proposing a dosing interval of every 12 hours for the Nap component of their FDC. The numbering of our rationale corresponds to the numbering directly above.

1. We cannot rely on data about the plasma concentration of 15 µg/mL for a clinically meaningful analgesic effect from Study LAB693 of NDA 020204 due to concerns regarding the overall study design, methodology, and the Applicant's cross-study comparison to their Study RB5-US-1505. Therefore, the Applicant's BE data regarding maintaining a plasma concentration of 15,000 ng/mL for 11 to 12 hours cannot be utilized to support the proposed dosing interval. We also note that the purpose of Study LAB693 was for formulation development under NDA 020204, and not the determination of substantial evidence of effectiveness.

2. In the original NDA submission dated September 29, 2023, the Applicant did not have right of reference for NDA 021076, Aleve-D Sinus & Cold. Therefore, they could not rely on the dosing interval of every 12 hours from NDA 021076.

   On March 20, 2024, DNDP 1 issued an information request to the Applicant about their right of reference for NDA 021076. The Applicant responded with no patent infringement and their plan to now reference NDA 021076, in addition to NDA 020204.

   We reviewed the studies conducted under NDA 021076 to evaluate the dosing interval; Aleve-D Sinus & Cold caplets were indeed studied and dosed one caplet every 12 hours.

   Although the Applicant is now officially referencing NDA 021076 to support every 12-hour dosing interval, they did not provide for a scientific bridge between their product's naproxen component and the Nap 220 mg in Aleve-D Sinus & Cold, NDA 021076. Therefore, data on dosing interval from NDA 021076 cannot be utilized to support the dosing interval for the proposed FDC product.

3. In the Applicant's Naproxen Sodium Clinical Efficacy Section in Module 2.7.3.3.4 of NDA 217338, the efficacy data for naproxen sodium 250 and 440 mg dosed every 12 hours described in the studies are not applicable to the efficacy and dosing interval for the lower Nap 220 mg dosage proposed in the Applicant's FDC product.

DAAP's overall assessment of the Applicant's proposed dosing interval of two tablets every 12 hours is that the Applicant's rationale in their original NDA submission does not support the 12-hour dosing interval. At this time, the Applicant has not provided sufficient data, using a scientific bridge to NDA 021076, to compare their Nap component to Aleve-D Sinus & Cold, which is recommended to be taken every 12 hours.

Conclusion

For the Nap 220 mg component of the proposed FDC for NDA 217338, DAAP does not agree with the Applicant that a plasma concentration of 15,000 ng/mL equates to clinically meaningful benefit in pain reduction because the study, LAB693, that produced these data was flawed in design and methodology. Furthermore, it is difficult to draw any meaningful conclusions or comparisons of data between study LAB693 and the Applicant's Study RB5-US-1505 as bioanalytical methods have changed greatly in the last three decades.

The Applicant's proposed dosing interval for NDA 217338 is every 12 hours for their FDC product. The Applicant originally referenced Aleve 220 mg tablets (NDA 020204). Because Aleve is approved for dosing every 8-12 hours, it is possible that the proposed FDC may have waning efficacy between 8 and 12 hours in some patients. However, if the dosing interval for the FDC followed Aleve tablets, every 8 to 12 hours, the safety of re-dosing the other two FDC components of NDA 217338, dextromethorphan and guaifenesin, at 8 hours is unknown. The Applicant did not provide adequate data to support sustained efficacy of the naproxen component of the FDC for 12 hours. It is noted that during the NDA review cycle, the Applicant submitted their right of reference for Aleve-D Sinus & Cold (NDA 021076), that is dosed every 12 hours. However, since the Applicant has not provided an adequate scientific bridge from the Nap in their FDC to NDA 021076, the NDA 021076 cannot be utilized to support the proposed dosing interval of two tablets every 12 hours.

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/s/

TIMOTHY T JIANG
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NANCY C DICKINSON
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ALLA T BAZINI
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RIGOBERTO A ROCA
05/21/2024 02:32:39 PM

M E M O R A N D U M
Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: January 22, 2024

To: Nushin Todd, MD, Director, Division of Nonprescription Drugs I

Through: Dominic Chiapperino, PhD, Director, Controlled Substance Staff

From: Chad J. Reissig, PhD, Supervisory Pharmacologist
Controlled Substance Staff

Subject: **NDA 217338** for Mucinex 12 HR Cold & Fever Multi-Symptom (naproxen sodium 110 mg, dextromethorphan HBr 30 mg, and guaifenesin 600 mg) extended-release tablets
Indication: helps loosen phlegm (mucus) and thin bronchial secretions to rid the bronchial passageways of bothersome mucus and make coughs 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 the common cold
- temporarily reduces fever

Dosage and Route: Naproxen sodium 110 mg, dextromethorphan HBr 30 mg, and guaifenesin 600 mg extended-release oral tablets
Sponsor: RB Health
PDUFA Goal Date: July 29, 2024

Materials Reviewed: NDA submission 217338 and published literature (see references)

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I. EXECUTIVE SUMMARY

1. Background

This memorandum responds to a consult request by the Division of Nonprescription Drugs I (DNPDI) to evaluate the abuse potential of an extended-release combination drug containing Naproxen Sodium 110 mg, Dextromethorphan HBr 30 mg, and Guaifenesin 600 mg submitted by RB Health LLC in NDA 217338 for Mucinex 12 HR Cold & Fever Multi-Symptom. The drug product is indicated for the management of symptoms of the common cold and upper respiratory infections. The drug is being submitted under the 505(b)(2) pathway citing NDA 020204 (Aleve®) and NDA 021620 (Mucinex® DM extended-release tablets) as the reference listed drugs (RLD). This is the first time CSS has reviewed this product, although CSS has reviewed dextromethorphan (DXM)-containing products previously (e.g., NDA 215430 for AXS-05 containing DXM and bupropion, C. Reissig DARRTS review, 7/29/2021).

Dextromethorphan (DXM) has been marketed for over 40 years and is the active pharmaceutical ingredient (API) in several over-the-counter (OTC) cough suppressant medications. Despite its OTC availability and non-scheduled status, DXM is a known drug of abuse (Nordt, 1998; Tomczak et al., 2012). The primary mechanism of action of DXM is antagonism of N-methyl-D-aspartate (NMDA) receptors, a mechanism of action similar to ketamine and phencyclidine (PCP) (Church et al., 1994; Church et al., 1991) which are known drugs of abuse and scheduled under the Controlled Substances Act (CSA). Consistent with this mechanism of action, high-dose DXM studies in humans have demonstrated that DXM produces hallucinogenic effects and acute cognitive impairment (Carter et al., 2013; Reissig et al., 2012), although the subjective effects can be differentiated from classic serotonergic hallucinogens under select circumstances (Barrett et al., 2018; Carbonaro et al., 2020; Carbonaro et al., 2018). In a prior evaluation of DXM, results of which were communicated to the Drug Enforcement Administration (DEA) by HHS on October 4, 2017, levels of actual nonmedical use and resulting harms were considered to not warrant a recommendation for drug scheduling.

In the current NDA submission, according to the Sponsor, the product was developed based on existing products containing DXM and guaifenesin, and adds naproxen to:

> "…enhance the spectrum of symptoms that can be addressed by the product and to improve consumer convenience by reducing the number of individual products that would otherwise have to be taken. Therefore, the new combination is intended to help reduce the potential for confusion and safety concerns resulting from different

dosing regimens and active ingredients associated with the combination of several individual drug products."

2. Conclusions

- No components of Mucinex 12 HR Cold & Fever Multi-Symptom are scheduled under the Controlled Substances Act.
- High doses of dextromethorphan (DXM) produce psychedelic-like and dissociative effects that are associated with its abuse potential and recreational use.
- However, Mucinex 12 HR Cold & Fever Multi-Symptom does not contain an amount of DXM (i.e., 30 mg) that is greater than currently marketed DXM-containing products. Therefore, Mucinex 12 HR Cold & Fever Multi-Symptom does not present an increased abuse potential relative to existing, FDA-approved products containing DXM.

3. Recommendations

Based on our findings as captured in the Conclusions section, we recommend the following:

- Mucinex 12 HR Cold & Fever Multi-Symptom should not be controlled under the Controlled Substances Act (CSA).
- Section 9 ("Drug Abuse and Dependence") should not be included in the drug label.

II. Discussion

1. Chemistry

1.1 Substance Information

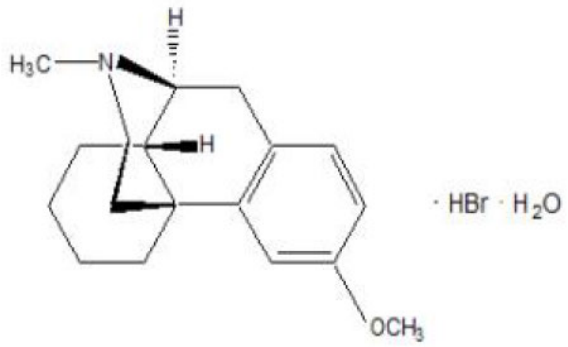
According to the Sponsor, the drug product is a modified release bi-layer tablet consisting of a (b) (4) modified release layer (MR) debossed with 'Mucinex', (b) (4) and a white immediate release layer (IR) (b) (4)

Naproxen sodium was first approved on January 11, 1994, has not shown an abuse potential, and will not be reviewed further in this memo.

The molecular formula of dextromethorphan is $C_{18}H_{25}NO \cdot HBr \cdot H_2O$ and it has a molecular weight of 370.3 g/mol. The CAS number for dextromethorphan is 6700-34-1 and the chemical names are:

- Ent-3-Methoxy-9a-methylmorphinan hydrobromide monohydrate
- 3-Methoxy-17-methyl-9α, 13α, 14α-morphinan hydrobromide monohydrate and
- (+)-3-Methoxy-9a-methylmorphinan hydrobromide monohydrate

The structure of dextromethorphan appears below:



2. Nonclinical Pharmacology

The Sponsor did not perform any abuse-related nonclinical pharmacology studies.

2.1 Safety Pharmacology/Metabolites

The published literature mentions three major metabolites of DXM: DXO, 3-hydroxymorphinan, and 3-methoxymorphinan (Barnhart, 1980). The metabolites of DXM are significant, notably, DXO (see section 2.4 below).

2.2 Animal Behavioral Studies

The Sponsor did not perform any abuse related animal studies. Both DXO and DXM are self-administered in PCP-trained monkeys (Nicholson et al., 1999; Young et al., 1981) and each substitute for PCP in PCP-trained rodents in drug discrimination studies. Similarly, PCP was able to completely substitute for DXM in DXM-trained rats (Holtzman, 1994). However, some human studies suggest that the subjective effects of DXM and DXO differ (Zawertailo et al., 1998; Zawertailo et al., 2010). These data suggest that DXM and PCP produce similar subjective effects, a finding consistent with DXM's NMDA antagonist properties.

3. Clinical Studies

A single clinical study was performed to support this 505(b)(2) application (study RB5-US-1505). The study was a relative bioavailability (BA) study comparing the new product (Mucinex 12 HR Cold & Fever Multi-Symptom) to the RLD (coadministration of Mucinex DM and Naproxen Sodium). The study title was:

> "An Open-Label, Randomized, Balanced, Single-Dose, Four-Treatment, Four- Period, Crossover Relative Bioavailability Study of an Experimental Combination Extended-Release Formulation of 600 mg Guaifenesin, 30 mg Dextromethorphan- Hydrobromide, and 110 mg Naproxen Sodium Bi-layer Tablets Compared to a Co-administration of Mucinex® DM and Naproxen Sodium Reference Products Under Fasted and Fed Conditions"

Healthy normal subjects aged 18-55 were enrolled in the study. Standard exclusion criteria were applied (e.g., pregnant women and subjects with clinically significant medical history were excluded). Once enrolled, subjects received 4 different treatments with a 10-day washout separating drug administrations. The four treatments (A-D) were as follows:

Treatment A: Two (b) (4) Tab tablets after 10-hour fast
Treatment B: Two (b) (4) Tab tablets after a high-fat meal
Treatment C: Two Mucinex® DM tablets co-administered with one Aleve® tablet after 10-hour fast
Treatment D: Two Mucinex® DM tablets co-administered with one Aleve® tablet after a high-fat meal

The primary study endpoints were: Cmax (maximum observed plasma concentration), AUC0-t (area under the plasma concentration versus time curve from zero to time t) and AUC0-inf (AUC extrapolated to infinite time). Secondary endpoints included: Tmax (time to maximum observed concentration), λz (apparent first order terminal rate constant), t1/2 (apparent terminal elimination half-life), Cl/F (apparent oral plasma clearance), Vd/F (apparent volume of distribution), AUCR (AUC0- t/AUC0-inf) and Cn (plasma concentration at each nominal time point). Adverse events (AEs) were also assessed. A total of 102 subjects participated in the study and 61 subjects (n=61) completed the study and received all four treatments. This study (study RB5-US-1505) was assessed for AEs associated with abuse potential and these appear in Table 1 below.

Table 1: Abuse-related Adverse Events from Study RB5-US-1505

	All subjects (N=102)	**Treatment A (N=83)**	**Treatment B (N=82)**	**Treatment C (N=79)**	**Treatment D (N=76)**
Preferred Term	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Feeling abnormal	3 (2.9)	1 (1.2)	1 (1.2)	0	1 (1.3)
Somnolence	1 (0.98)	0	0	0	1 (1.3)
Restlessness	1 (0.98)	0	0	1 (1.3)	0

As seen above, few abuse-related AEs occurred and, for the majority of preferred terms generating an AE, an event occurred in only a single subject, regardless of dose. In addition, there were no AEs of "euphoric mood" or hallucination that might be expected with an NMDA antagonist like DXM. However, it is notable that prior clinical studies of DXM produced effects often sought in a context of nonmedical use, although the doses in these prior studies were much higher (e.g., 400 mg) than those examined in this BA study.

III. References

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 11/7/2023

TO: Division of Nonprescription Drugs I (DNPD I)
Office of Nonprescription Drugs (ONPD)

FROM: Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Decline to conduct on-site inspections**

RE: NDA 217338

The Office of Study Integrity and Surveillance (OSIS) determined that inspections are not needed for the sites listed below. The rationale for this decision is noted below.

Rationale

QPS Bio-Kinetic, Springfield: The Office of Regulatory Affairs (ORA) conducted an inspection for the clinical site in November 2022. The inspection was conducted under the following submission: BLA 761279.

OSIS concluded that data from the reviewed studies were reliable.

(b) (4): OSIS conducted a Remote Regulatory Assessment (RRA) for the analytical site in (b) (4). The RRA was conducted under the following submissions: BLA NON-RESPONSIVE and NDAs NON-RESPONSIVE.

OSIS concluded that data from the reviewed studies were reliable.

Sites

Facility Type	Facility Name	Facility Address
Clinical	QPS Bio-Kinetic Clinical Applications, LLC.	1816/1820 West Mount Vernon Street, Springfield, MO
Analytical	(b) (4)	

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