Integrated Review

Table 1. Application Information

Application type	NDA
Application number(s)	217338
Priority or standard	Standard
Submit date(s)	9/29/2023
Received date(s)	9/29/2023
PDUFA goal date	7/29/2024
Division/office	Division of Nonprescription Drugs I (DNPD I)
Review completion date	7/29/2024
Established/proper name	Guaifenesin, dextromethorphan hydrobromide and naproxen sodium
(Proposed) proprietary name	Mucinex 12 HR Cold & Fever Multi-Symptom
Pharmacologic class	Expectorant, antitussive, analgesic/antipyretic
Other product name(s)	(b) (4)
Applicant	RB Health (US) LLC
Dosage form(s)/formulation(s)	Extended-release tablets
Dosing regimen	• Adults and children 12+: Take 2 tablets every 12 hours. Not to exceed 4 tablets per 24 hours. • Children under 12 years of age: Do not use.
Applicant-proposed indication(s)/ population(s)	• Helps loosen phlegm (mucus) and thin bronchial secretions to rid the bronchial passageways of bothersome mucus and make coughs more productive • Temporarily relieves o Cough due to minor throat and bronchial irritation as may occur with the common cold or inhaled irritants o The intensity of coughing o The impulse to cough to help you get to sleep o Minor aches and pains due to headache and the common cold • Temporarily reduces fever
SNOMED CT code for proposed indication disease term(s)[1]	22253000 Pain (finding), 386661006 Fever (finding), 417850002 Respiratory tract congestion and cough (disorder), 82272006 Common Cold (disorder)
Regulatory action	Complete response
Approved dosage (if applicable)	N/A, complete response
Approved indication(s)/ population(s) (if applicable)	N/A
SNOMED CT code for approved indication disease term(s)[1]	N/A

[1] For internal tracking purposes only.
Abbreviations: PDUFA, Prescription Drug User Fee Act; SNOMED CT, Systematized Nomenclature of Medicine Clinical Terms

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Glossary

ADAM	advanced dissolution, absorption, and metabolism
AE	adverse event
AUC	area under the concentration-time curve
AUC_{inf}	area under the concentration-time curve estimated to infinity
AUC_{0-t}	area under the concentration-time curve up to the last measurable concentration
BA	bioavailability
BE	bioequivalence
CFR	Code of Federal Regulations
CI	confidence interval
CL_{iv}	plasma clearance
C_{max}	maximum plasma concentration
COVID-19	coronavirus disease 2019
CSS	Controlled Substance Staff
CV	cardiovascular
DAAP	Division of Anesthesiology, Addiction Medicine, and Pain Medicine
DFL	Drug Facts label
ER	extended-release
FAERS	FDA Adverse Event Reporting System
FDA	Food and Drug Administration
FDC	fixed dose combination
GI	gastrointestinal
HBr	hydrobromide
IND	investigational new drug
IR	immediate-release
MR	modified release
NDA	new drug application
NPDS	National Poison Data System
NSAID	nonsteroidal anti-inflammatory drug
OPQ	Office of Pharmaceutical Quality
OSIS	Office of Study Integrity and Surveillance
PBPK	physiological-based pharmacokinetics
PD	pharmacodynamic
PDP	Principal Display Panel
PK	pharmacokinetic
PT	preferred term
SOI	statement of identity
TEAE	treatment-emergent adverse event
T_{max}	time to maximum concentration
USP	United States Pharmacopeia
VBE	virtual bioequivalent
V_{ss}	volume of distribution
WHO	World Health Organization

I. Executive Summary

1. Summary of Regulatory Action

Reckitt Benckiser LLC (hereinafter referred to as the Applicant, RB Health) submitted a new drug application (NDA) 217338 pursuant to section 505(b)(2) of the Federal Food, Drug and Cosmetic Act on September 29, 2023. The Applicant seeks marketing approval for Mucinex 12 HR Cold & Fever Multi-Symptom (guaifenesin 600 mg, dextromethorphan hydrobromide 30 mg, and naproxen sodium 110 mg) extended-release (ER) tablet for nonprescription use. 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 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 and temporarily relieves fever. The proposed dosing instruction for this fixed dose combination (FDC) ER formulation is to take two tablets every 12 hours.

This NDA was reviewed by a multidisciplinary review team consisting of members from the Division of Nonprescription Drugs I, the Division of Inflammation and Immune Pharmacology, the Office of Pharmaceutical Quality, and the Office of Nonprescription Drugs-Pharmacology/Toxicology. In addition, the Division of Anesthesiology, Addiction Medicine, and Pain Medicine, the Division of Neuropsychiatric Pharmacology, the Office of New Drug Policy, and the Controlled Substance Staff were consulted.

The regulatory action is a complete response.

The major deficiency that precludes approvability of this application is insufficient evidence to support the proposed 12-hour duration of action and dosing regimen for this ER product. To support efficacy of the proposed product, the Applicant conducted a clinical pharmacology program to establish bioequivalence (BE) of its proposed product to the listed drugs, Mucinex DM (guaifenesin 600 mg/dextromethorphan hydrobromide 30 mg tablets, NDA 021620) and Aleve (naproxen sodium tablets 220 mg, NDA 020204). Although the Applicant demonstrated BE between each component of its proposed FDC product and those of Mucinex DM and Aleve, the proposed product's dosing instruction is to take a dose every 12 hours, which represents a modification of the dosing instruction for Aleve. The Directions section of the Drug Facts label for Aleve state, in part: take 1 tablet every 8 to 12 hours while symptoms last; for the first dose you may take 2 tablets within the first hour; do not exceed 2 tablets in any 8- to 12-hour period; do not exceed 3 tablets in a 24-hour period. The concern is that the naproxen component of the FDC product may not last the entire 12 hours, and pain and fever may return before it is time to redose (per the proposed Drug Facts label directions and the proposed proprietary name which includes the proposed dosing interval [i.e., 12 Hour]). The proposed dosing interval cannot be supported solely by demonstrating BE to Mucinex DM and Aleve.

The Applicant has not provided adequate additional data to support the 12-hour-only dosing interval for the naproxen component of its proposed product. This concern was raised during a

pre-NDA meeting with the Applicant on June 5, 2023. Additionally, during the review of this NDA, this issue was communicated to the Applicant (on December 11, 2023, and March 20, 2024). The Applicant's responses did not contain additional efficacy data to justify the 12-hour-only dosing interval for the proposed product; rather, they focused on pharmacokinetic (PK) and pharmacodynamic results from Aleve under NDA 020204. Additionally, late in the review cycle, the Applicant indicated their reliance upon an additional listed drug, Aleve-D Sinus and Cold (naproxen sodium 220 mg and pseudoephedrine hydrochloride 120-mg tablets, NDA 021076) to support efficacy of a 12-hour dosing interval for the naproxen component. The Applicant proposed to create an indirect PK bridge relying upon the Aleve-D listed drug based on PK data retrieved from FDA reviews.

These justifications were reviewed by members of Division of Nonprescription Drugs I, Division of Anesthesiology, Addiction Medicine, and Pain Medicine, Division of Inflammation and Immune Pharmacology, Division of Neuropsychiatric Pharmacology, and Office of New Drug Policy. There was agreement that the Applicant did not provide adequate justification for a 12-hour-only dosing interval. Additionally, while Aleve-D Sinus and Cold is a naproxen-containing product that is approved to be used every 12-hours, the Applicant has not established an adequate bridge to justify reliance upon FDA’s previous finding for the listed drug. Reference to FDA’s prior reviews for Aleve-D is not an appropriate source of information that can be relied upon in support of a 505(b)(2) NDA, nor has the Applicant obtained a right of reference to the data for Aleve-D to support approval of its proposed product. For detailed information supporting the basis for this complete response, please refer to the detailed reviews included in this Interdisciplinary Assessment document.

2. Benefit-Risk Assessment

2.1. Benefit-Risk Framework

Table 2. Benefit-Risk Framework

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of condition	• The common cold is one of the most frequently occurring illnesses that affect millions of Americans annually (Heikkinen and Järvinen 2003). • Colds can be caused by more than 200 different respiratory viruses (Eccles 2023). • Routine diagnosis by virology is neither feasible nor pragmatic given the sheer number of causative viruses and high incidence rate; nonetheless, specific diagnosis is not medically necessary. Laypersons' familiarity with the symptoms of the common cold makes it a self-diagnosable condition (Eccles 2023). • Symptoms of the common cold may include cough, mucus production, minor aches and pains, headache, and fever among other symptomatology. • Though they are self-limited and generally not considered a serious medical condition, colds can be bothersome to consumers and affect quality of life. • The high incidence of the common cold imposes a great economic burden in terms of increased healthcare seeking behaviors and lost productivity. The economic cost of infections caused by the common cold has been estimated to be $40 billion annually in the United States (Fendrick et al. 2003).	• The common cold affects millions of Americans annually. • Symptoms caused by the common cold can be uncomfortable and can temporarily affect quality of life. • Symptoms associated with the common cold are generally self-diagnoseable and self-manageable for lay consumers.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current treatment options	• Nonprescription medications indicated for the common cold may relieve some symptoms of the condition though they do not prevent, cure, or shorten the duration of illness. • A wide selection of nonprescription drug options is currently available for relief of a variety of different symptoms associated with the common cold. This includes single ingredient products as well as combination products that are allowed under the OTC Monograph M012 and those approved under section 505(b) of the Federal Food, Drug, and Cosmetic Act.	• Consumers rely on available safe and effective nonprescription drugs for symptomatic relief of symptoms associated with the common cold. • A variety of treatment options is currently available for multisymptom management of the common cold.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	• The proposed FDC product is intended to provide the convenience of having three ingredients that target different symptoms in one product that is dosed every 12 hours. • In a comparative pivotal PK study, the proposed FDC product demonstrated BE of each of its three active ingredients with those of the approved listed drugs, Mucinex DM (guaifenesin/dextromethorphan HBr) and Aleve (naproxen sodium), in both fasted and fed conditions. • The proposed FDC product's dosing instruction of every 12 hours is identical to the dosing interval for Mucinex DM; however, it differs from the dosing interval of the listed naproxen product. Aleve has a dosing interval of every 8-12 hours and directions that allow for a loading dose of two tablets for the first dose. The proposed difference in dosing interval for the naproxen component is not supported by demonstration of BE to Aleve. • A key uncertainty is whether consumers could lose analgesic or antipyretic efficacy of the naproxen component given the fixed 12-hour dosing of the proposed product. A concern is whether this would translate to a potential for consumer error in redosing the product prematurely, which could lead to overdose of the guaifenesin and dextromethorphan components, or whether consumers may choose to use the product with another analgesic, which could be problematic if another NSAID is used. • The proposed FDC product's dosing instruction of every 12 hours as well as its naproxen dose are identical to that of Aleve-D Sinus and Cold. The Applicant provided rationale to support an indirect bridge to this LD; however, the information was obtained from FDA reviews of NDA 021760, which are not considered appropriate sources of information that may be relied upon in support of a 505(b)(2) NDA.	• The proposed FDC product would present consumers with another alternative for nonprescription management of symptoms caused by the common cold. • The Applicant has not provided sufficient data to support its proposed dosing interval for the naproxen component. There are unresolved concerns that the proposed FDC product may not provide a duration of pain and fever relief necessary to support every 12-hour dosing.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and risk management	• Single ingredient products containing guaifenesin, dextromethorphan HBr, and naproxen sodium have been marketed as nonprescription drugs for decades. • The safety profile for each active ingredient is well characterized. • The safety data from the clinical program showed a small number of AEs overall and no SAEs. The AEs noted were generally mild and self-limited. The AE profile of the proposed product appeared similar to that of the approved listed treatment arms when taken concomitantly. • In the postmarketing safety data evaluating cases reporting concomitant use of all three active ingredients, there were generally few cases identified and among those, few were considered serious or involved fatal outcomes. Fatal cases were generally confounded by the involvement of multiple concomitant drugs. • Dextromethorphan is a known drug of abuse; however, the dose presented in the proposed FDC product is no greater than that present in already approved nonprescription dextromethorphan products. There were no findings in the clinical program that indicated an increased abuse potential.	• There were no SAEs or significant safety findings from the clinical program for this FDC product. • There were no significant findings in the postmarketing safety data when looking at concomitant use of all three active ingredients. • The dose of dextromethorphan HBr in the proposed FDC product is not greater than that of currently marketed products containing this ingredient and does not present an increased abuse potential relative to existing products.

Abbreviations: AE, adverse events; BE, bioequivalence; DM, dextromethorphan; FDA, Food and Drug Administration; FDC, fixed dose combination; HBr, hydrobromide; LD, listed drug; NDA, new drug application; NSAID, nonsteroidal anti-inflammatory drug; OTC, over-the-counter; PK, pharmacokinetic; SAE, serious adverse events

2.2. Conclusions Regarding Benefit-Risk

Each year, millions of Americans suffer from symptoms related to the common cold. Colds comprise a significant public health burden in the United States and are a major driver for consumers to seek self-care. Many nonprescription products are available for the relief of cold symptoms, including the use of single ingredient products targeted toward individual symptoms or combinations thereof. Notably, combination products containing an analgesic/antipyretic, cough medicine, and expectorant are available on the market (see Table 4). The proposed FDC ER tablet containing naproxen sodium 110 mg, dextromethorphan hydrobromide 30 mg, and guaifenesin 600 mg represents an additional treatment option for multisymptomatic relief of the common cold in the nonprescription setting.

The submitted data do not provide substantial evidence of efficacy to support the proposed 12-hour duration of action and dosing regimen. The Applicant has provided data to demonstrate that each component of its proposed FDC product is BE with that from approved listed drugs, Mucinex DM (NDA 021620) and Aleve (NDA 020204). However, the proposed 12-hour dosing regimen represents a modification from the approved dosing instruction of Aleve tablets: "take 1 tablet every 8 to 12 hours, for the first dose may take 2 tablets within the first hour." The Applicant provided several justifications including an indirect bridge to an additional listed drug, Aleve-D Sinus and Cold (NDA 021076), which is a naproxen-containing FDC product approved with a 12-hour dosing regimen. The review team has concluded that the Applicant has not provided adequate data to support a modification of dosing interval for the naproxen component.

Without definitive evidence supporting that the naproxen component of the proposed FDC product has a duration of action of 12 hours, concerns remain about the potential for waning or loss of analgesic and antipyretic effects of naproxen before the next dosing period. If pain or fever returns before the next dose, consumers may choose to take additional doses of the proposed FDC drug before 12 hours or they may choose to take another nonsteroidal anti-inflammatory drug product concomitantly until the desired effect occurs. Use of additional doses of the proposed FDC product could potentially lead to overdose of the guaifenesin and dextromethorphan components. Use of additional concomitant nonsteroidal anti-inflammatory drugs can be associated with serious adverse events that can occur with increased nonsteroidal anti-inflammatory drug use, including typical class effects of gastrointestinal bleeding risk, cardiovascular risk (anti-platelet effects), and hepatic and renal effects, all of which are known to be dose-related. The safety data submitted in this application came from a pivotal comparative bioavailability study and a review of postmarketing data for the concomitant use of the three active ingredients. These data do not address the potential for premature waning or loss of efficacy for the naproxen component and the outlined safety concerns.

In light of the outlined efficacy- and safety-related uncertainties and given the availability of multiple other therapies in the nonprescription setting intended for relief of symptoms associated with the common cold, benefit/risk profile for this product is unfavorable.

To address these concerns, the Applicant may consider the following approaches, among others (this list is not exhaustive):

- Provide clinical efficacy data to support a 12-hour duration of use when studied in a relevant patient population, or

- Conduct a PK study to establish a scientific bridge between the proposed product and NDA 021076 Aleve-D Sinus and Cold.

II. Interdisciplinary Assessment

3. Introduction

RB Health proposes to market an extended-release (ER) expectorant, antitussive, and analgesic/antipyretic fixed dose combination (FDC) tablet containing guaifenesin 600 mg, dextromethorphan hydrobromide (HBr) 30 mg, and naproxen sodium 110 mg for nonprescription use.

All three active ingredients of this combination drug product have extensive marketing history as single active ingredient drug products in the nonprescription setting. Naproxen has been marketed in the nonprescription setting since the 1994 approval of new drug application (NDA) 020204. Both dextromethorphan and guaifenesin have been marketed for over 50 years and are permitted ingredients in immediate-release (IR) products covered under the Over-the-Counter (OTC) Monograph M012: Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products for Over-the-Counter Human Use. OTC Monograph M012 also specifies that combinations of any single monograph oral antitussive active ingredient (such as dextromethorphan or dextromethorphan HBr) with any single expectorant active ingredient (such as guaifenesin) is to be a permitted combination. As the OTC Monograph M012 does not include provisions for ER formulations, an ER version of guaifenesin/dextromethorphan HBr (Mucinex DM) was first approved under NDA 021620 in 2004. The Applicant is the marketing authorization holder for Mucinex DM.

While a combination of an expectorant, antitussive, and analgesic/antipyretic is not novel for the nonprescription setting, the specific combination of the proposed ingredients is novel for the U.S. and global market. The proposed product is intended to relieve multiple symptoms associated with the common cold for adults and children older than 12 years. The Applicant is relying on FDA's previous findings of safety and efficacy for NDA 020204 Aleve (naproxen sodium 220 mg) tablets, NDA 021620 Mucinex DM (guaifenesin/dextromethorphan HBr 600 mg/30 mg) ER tablets, and NDA 021076 Aleve-D Sinus and Cold (naproxen sodium/pseudoephedrine hydrochloride 220 mg/120 mg) tablets. Of note, the latter of the three listed drugs was added after submission of the NDA.

The Applicant has proposed the proprietary name "Mucinex 12 HR Cold & Fever Multi-Symptom." 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 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 relieves fever

The proposed bilayer combination product comprises a white IR layer (b) (4) (b) (4) (b) (4) and a (b) (4) modified release (MR) layer debossed with "Mucinex" (b) (4) The proposed dosing instruction is to take two tablets every 12 hours.

Therapeutic Context: Analysis of Condition

The common cold is one of the most common illnesses that affect Americans each year. Colds are caused by viruses and are typically characterized by a constellation of symptoms, which may include rhinorrhea, nasal congestion, sore throat, sneezing, cough, malaise, headache, and fever. These symptoms are generally self-diagnosable and self-manageable and typically peak within 1-3 days and last 7-10 days (Heikkinen and Järvinen 2003; Arroll 2011). Colds are usually self-limited illnesses and are unlikely to cause mortality or serious morbidity in healthy individuals. Nevertheless, symptoms caused by the common cold can be uncomfortable and can temporarily affect quality of life.

The common cold affects millions of Americans annually with adults experiencing an average of 2-4 episodes a year and children experiencing an average of 6-8 episodes a year (Heikkinen and Järvinen 2003). The National Institute of Allergy and Infectious Disease estimated that individuals in the United States suffer more than 1 billion colds annually (Wein 2009). Though generally not considered a serious medical condition, the high incidence of colds imposes a great economic burden in terms of increased healthcare seeking behaviors and lost productivity. The economic cost of the common cold is estimated to be $40 billion annually (Fendrick et al. 2003).

Analysis of Current Treatment Options

There is a wide selection of combination nonprescription drug options intended for relief of multiple symptoms associated with the common cold. These different combination drug products aim to provide consumers greater convenience by combining different active ingredients that target different symptoms in a single product. A myriad of nonprescription options that combine analgesics/antipyretics with cough and cold ingredients, which are listed in Table 3 (NDA approved products) and Table 4 (monograph drug products). Due to the large number of monograph cough and cold combination products, the compiled lists are limited to include oral combination products containing an analgesic/antipyretic for adults and children 12 years and older and exclude products containing phenylephrine.

Table 3. Summary of NDA Approved Oral Treatment Options for Nonprescription Multi-Symptom Cough and Cold Combination Products Containing an Analgesic/Antipyretic for Adults and Children 12 Years and Older

Product Name	Active Ingredients and Dose	Purpose	Route, Dosage Form, and Dosing Instructions
Advil Cold and Sinus	• Ibuprofen 200 mg • Pseudoephedrine HCl 30 mg	• Pain reliever/fever reducer • Nasal decongestant	Oral capsule: 1 capsule every 4 – 6 hours

Product Name	Active Ingredients and Dose	Purpose	Route, Dosage Form, and Dosing Instructions
Advil Cold and Sinus	• Ibuprofen 200 mg • Pseudoephedrine HCl 30 mg	• Pain reliever/fever reducer • Nasal decongestant	Oral caplet: 1 caplet every 4 – 6 hours
Aleve-D Sinus and Cold	• Naproxen sodium 220 mg • Pseudoephedrine HCl 120 mg	• Pain reliever/fever reducer • Nasal decongestant	Oral caplet: 1 caplet every 12 hours

Source: Generated by reviewer from information collected on DailyMed and FDALabel
Note that phenylephrine containing products have not been included in this table.
Abbreviations: HCl, hydrochloride; mg, milligram; NDA, new drug application

Table 4. Summary of OTC Monograph Multi-Symptom Cough and Cold Combination Oral Products Containing an Analgesic/Antipyretic for Adults and Children 12 Years and Older

Active Ingredients	Purpose	Dosage Form(s)
Acetaminophen, Dextromethorphan HBr	• Pain reliever/fever reducer • Cough suppressant	Tablet, capsule, solution
Acetaminophen, Chlorpheniramine maleate	• Pain reliever/fever reducer • Antihistamine	Tablet, capsule
Acetaminophen, Guaifenesin	• Pain reliever/fever reducer • Expectorant	Capsule, solution
Acetaminophen, Dextromethorphan HBr, Guaifenesin	• Pain reliever/fever reducer • Cough suppressant • Expectorant	Capsule, solution
Acetaminophen Dextromethorphan HBr, Doxylamine succinate	• Pain reliever/fever reducer • Cough suppressant • Antihistamine	Tablet, capsule, solution
Acetaminophen Dextromethorphan HBr, Chlorpheniramine maleate	• Pain relief/ fever reducer • Cough suppressant • Antihistamine	Tablet, solution
Acetaminophen Dextromethorphan HBr, Diphenhydramine	• Pain relief/ fever reducer • Cough suppressant • Antihistamine	Solution
Acetaminophen Dextromethorphan HBr, Pseudoephedrine HCl	• Pain reliever/fever reducer • Cough suppressant • Nasal decongestant	Tablet

Active Ingredients	Purpose	Dosage Form(s)
Acetaminophen Dextromethorphan HBr, Chlorpheniramine, Pseudoephedrine HCl	• Pain reliever/fever reducer • Cough suppressant • Antihistamine • Nasal decongestant	Tablet
Acetaminophen Dextromethorphan HBr, Guaifenesin, Pseudoephedrine HCl	• Pain reliever/fever reducer • Cough suppressant • Expectorant • Nasal decongestant	Tablet

Source: Generated by reviewer from information collected on DailyMed and FDALabel
Note: Phenylephrine containing products have not been included in this table.
Abbreviations: HBr, hydrobromide; HCl, hydrochloride; OTC, over-the-counter

Clinical Development Program

The Applicant conducted the clinical development program under investigational new drug (IND) application 105403. An initial meeting was held on May 4, 2011, between RB Health and FDA to discuss the development program. FDA agreed that the proposed combination may be rational for target populations with upper respiratory infection symptoms including cough, fever, and pain. Additionally, three more meetings were held including a pre-NDA milestone meeting. A key recommendation highlighted during these meetings was the need for the Applicant to support the combination product's proposed dosing instruction to take two tablets every 12 hours. While the 12-hour dosing interval was the same as that for Mucinex DM, it differed from that of Aleve, which has a dosing interval of every 8 to 12 hours. In a Type C meeting (meeting minutes dated September 10, 2015), FDA agreed that the proposed pharmacokinetic (PK) program relying on Mucinex DM and Aleve appeared reasonable, but noted that the Applicant needed to "demonstrate that the PK profiles will support a 12-hour dosing regimen." FDA reiterated this point in a March 7, 2016, Written Response Only meeting. In the Type B pre-NDA meeting held on June 5, 2023, FDA highlighted the potential issue again. FDA inquired what consumers were supposed to do if their pain or fever returned prior to the 12 hours necessary before the next dosing. FDA advised the Applicant to provide data or information to support a fixed 12-hour dosing interval.

In the NDA filing letter dated December 11, 2023, FDA notified the Applicant that during the filing review, a potential review issue was the difference in the dosing intervals between the combination product and the approved listed drug Aleve. FDA requested that the Applicant provide further data or information specific to support both pain and fever indications for the entire 12-hour dosing interval for the proposed product. Among other rationale, the Applicant provided justification that NDA 021076 Aleve-D Sinus and Cold was a naproxen-containing product that had been approved with a 12-hour dosing interval. In an Information Request dated March 20, 2024, FDA noted that if the Applicant's intention was to rely upon NDA 021076, then it would need to specify its reliance on NDA 021076 formally, and provide further information to establish a scientific bridge between the proposed FDC product and the relied-upon listed drug. In an April 12, 2024 response to the Information Request, the Applicant added NDA 021076 Aleve-D Sinus and Cold as a relied upon listed drug and provided rationale to establish an indirect PK bridge based on PK data retrieved from FDA reviews.

Further information on key meetings, dates, and discussion points is provided in greater detail in Section 12.

3.1. Review Issue List

3.1.1. Key Efficacy Review Issues

3.1.1.1. Duration of Action Considerations and 12-Hour Dosing Regimen

Refer to Section 6.3.1.

3.1.2. Key Safety Review Issues

3.1.2.1. Clinical Safety of the Proposed Product

Refer to Section 7.7.1.

3.1.2.2. Safety Data from Postmarketing Safety and Literature Review Support Safe Use of the Proposed Product

Refer to Section 7.7.2.

3.1.2.3. Proposed Product Does Not Present an Increased Risk for Dextromethorphan Abuse

Refer to Section 7.7.3.

3.2. Approach to the Clinical Review

To support efficacy of the proposed product, the Applicant relies upon the established clinical efficacy of guaifenesin and dextromethorphan HBr from NDA 021620 (Mucinex DM), and naproxen sodium from NDA 020204 (Aleve) and NDA 021076 (Aleve-D Sinus and Cold).

The Applicant conducted a PK program to establish bioequivalence (BE) of its proposed product to the listed drugs, Mucinex DM and Aleve, in healthy adult subjects. Study RB5-US-1505 is considered the pivotal relative bioavailability (BA) study supporting efficacy of this combination product (see Section 5.2 for a high-level summary of this information and Section 14 for a full clinical pharmacology review).

FDA requested that the Applicant provide data or information to support the difference in the proposed dosing interval (i.e., 12 hours) for this combination product and the approved dosing interval (i.e., 8 to 12 hours) of the listed product NDA 020204 Aleve. The Applicant did not

conduct new clinical efficacy studies to demonstrate the duration of action of its proposed drug product, rather provided several justifications including rationale to establish an indirect PK bridge to a third listed drug (NDA 021076). Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP) and Division of Neuropsychiatric Pharmacology were consulted to address the Applicant's justifications to support the proposed dosing interval for a naproxen product (see Section 6.3.1).

The safety of the proposed product is supported by the clinical safety data generated from the pivotal PK Study RB5-US-1505 (see Section 7.6.1). In addition, the Applicant provided analyses of postmarketing safety data associated with the concomitant use of each of the three active ingredients primarily from RB Health's own pharmacovigilance program as well as FDA Adverse Event Reporting System (FAERS), World Health Organization (WHO) VigiBase, National Poison Data System (NPDS), and the published literature (see Section 7.6.2).

Additionally, because the proposed product would be the first new nonprescription NDA product to contain dextromethorphan in 20 years, the Controlled Substance Staff (CSS) was consulted to evaluate the abuse potential of the proposed ER combination drug containing dextromethorphan HBr (see Section 7.7.3 for more details).

4. Patient Experience Data

Table 5. Patient Experience Data Submitted or Considered

Data Submitted in the Application		
Check if Submitted	**Type of Data**	**Section Where Discussed, if Applicable**
Clinical Outcome Assessment Data Submitted in the Application		
☐	Patient-reported outcome	
☐	Observer-reported outcome	
☐	Clinician-reported outcome	
☐	Performance outcome	
Other Patient Experience Data Submitted in the Application		
☐	Patient-focused drug development meeting summary	
☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel)	
☐	Observational survey studies	
☐	Natural history studies	
☐	Patient preference studies	
☐	Other: (please specify)	
☒	If no patient experience data were submitted by Applicant, indicate here.	
Data Considered in the Assessment (But Not Submitted by Applicant)		
Check if Considered	**Type of Data**	**Section Where Discussed, if Applicable**
☐	Perspectives shared at patient stakeholder meeting	
☐	Patient-focused drug development meeting summary report	
☐	Other stakeholder meeting summary report	
☐	Observational survey studies	
☐	Other: (please specify)	

5. Pharmacologic Activity, Pharmacokinetics, and Clinical Pharmacology

5.1. Nonclinical Assessment of Potential Effectiveness

No nonclinical data were generated for the assessment of potential effectiveness.

5.2. Clinical Pharmacology/Pharmacokinetics

Background

The Applicant conducted one pivotal relative BA Study RB5-US-1505 to compare the PK and assess the effects of the proposed drug product and two of the listed drugs, NDA 020204 Aleve and NDA 021620 Mucinex DM, to support the scientific bridge of this 505(b)(2) application. In addition, two pilot studies, 2009-GGE-TRI-DM and 2014-MUCDM-NAP-02, were also submitted under this NDA. The outcomes of these two pilot studies were applied to help design the pivotal Study RB5-US-1505.[1] In addition, the Applicant submitted a physiological-based pharmacokinetics (PBPK) model (i.e., RECK-5B report) to support the extrapolation of adult PK results to adolescents.

Although the proposed doses of the three active ingredients were the same as the doses used in the listed drugs, the proposed dosing regimens are slightly different, which are described in Table 6.

Table 6. Dosing Regimen of the Proposed Drug, Mucinex DM, and Aleve

Age Group and Prandial Condition	Proposed (NDA 217338)	Mucinex DM (NDA 021620)	Aleve (NDA 020204)
Regimen in adults and children over 12 years of age	Take 2 tablets every 12 hours. Do not exceed 4 tablets within 24 hours.	Take 2 tablets every 12 hours. Do not exceed 4 tablets within 24 hours.	Take 1 tablet every 8 to 12 hours while symptoms last. For the first dose you may take 2 tablets within the first hour. Do not exceed 2 tablets in any 8- to 12-hour period. Do not exceed 3 tablets in a 24-hour period.
Regimen in children below 12 years of age	Do not use.	Do not use.	(b) (4)
Instructions with regard to food	Take with food or milk if stomach upset occurs.	Can be taken without regard for timing of meals.	Take with food or milk if stomach upset occurs.

Source: Reviewer generated from approved labels of NDA 020204 and NDA 021620.
Abbreviations: DM, dextromethorphan; NDA, new drug application

On April 12, 2024, the Applicant amended the NDA to include Aleve-D Sinus and Cold (naproxen sodium 220 mg and pseudoephedrine hydrochloride 120 mg ER tablet, NDA 021076) as a listed drug, which leveraged an indirect PK bridge for every 12-hour dosing frequency of the naproxen component of the proposed product as every 12-hour is the only dosing frequency approved under NDA 021076.[2] Aleve-D Sinus and Cold is indicated for multisymptom relief of sinus pressure, headache, sinus, congestion, nasal congestion, body aches, and fever.

[1] Note that the pilot studies were conducted using a different formulation than the to-be-marketed formulation.
[2] CDSESUB1\EVSPROD\nda217338\0015\m1\us\12-cov-let\cover.pdf

Of note, the basis for approval of NDA 021620 Mucinex DM was via PK bridging with Mucinex and Vicks Formula 44. However, clinical efficacy and safety studies were conducted to support the other two listed drugs (NDA 020204 Aleve and NDA 021706 Aleve-D Sinus and Cold).[3]

The major clinical pharmacology review tasks for this 505(b)(2) application were to assess:

- Whether the pivotal relative BA study demonstrates BE of the three active ingredients between the proposed drug product and the listed drugs.
- The food effect on the proposed drug product.
- The scientific bridge between the proposed drug product and the listed drugs.
- The necessity and adequacy of the PBPK modeling and simulation analysis to support the extrapolation of PK from adults to adolescents.

Assessment

Bioequivalence of the Three Active Ingredients Between the Proposed Product and the Listed Drugs (NDA 020204 Aleve and NDA 021620)

Pivotal Study RB5-US-1505 was an open-label, randomized, balanced, single-dose, four-treatment, four-period, crossover relative BA study of the to-be-marketed formulation of proposed drug product containing 600 mg guaifenesin, 30 mg dextromethorphan HBr, and 110 mg naproxen sodium bilayer tablets in comparison with co-administration of the listed drugs (NDA 020204 Aleve naproxen sodium 220-mg tablets) and NDA 021620 (Mucinex DM dextromethorphan HBr 30 mg and guaifenesin 600 mg ER tablets) under fasted and fed conditions. Each subject received a total dose of 1200 mg of guaifenesin, 60 mg of dextromethorphan HBr, and 220 mg of naproxen sodium in each of following treatment periods:

- Treatment A: Two Mucinex 12 HR Cold & Fever Multi-Symptom tablets after a 10-hour fast
- Treatment B: Two Mucinex 12 HR Cold & Fever Multi-Symptom after a high-fat meal
- Treatment C: Two Mucinex DM tablets and one Aleve tablet after a 10-hour fast
- Treatment D: Two Mucinex DM tablets and one Aleve tablet after a high-fat meal

In this study under fasted condition, BE was established for all three active ingredients between the proposed drug product (Treatment A) and the listed drugs Mucinex DM and Aleve (Treatment C), as the 90% confidence interval of geometric mean ratios of area under the concentration-time curve (AUC) up to the last measurable concentration, AUC estimated to infinity, and maximum plasma concentration (C_{max}) of dextromethorphan, guaifenesin, and naproxen were all within the range of 0.8 to 1.25. (Refer to Section 14.2.1 at Table 24 (dextromethorphan), Table 27 (guaifenesin), and Table 30 (naproxen) for detailed PK analyses.

Food Effect

Study RB5-US-1505 demonstrated that food has no apparent effect on systemic exposure of guaifenesin and naproxen for the proposed drug product, as BE was established for guaifenesin and naproxen with or without co-administration of a high-fat meal. A high-fat meal increased the

[3] Refer to the Section 14 for additional information on approval basis for the listed drugs

C_{max} and AUC_{inf} of dextromethorphan of the proposed drug product by 34% and 24%, respectively (Table 26). Meanwhile, a similar food effect of an increase of dextromethorphan exposure was observed when following the administration of the listed drug (i.e., NDA 021620 Mucinex DM). Thus, this finding supports the proposed prandial condition for the combination drug indicating that the product can be taken regardless of food.

The Scientific Bridge Between the Proposed Drug Product and the Listed Drugs

From the clinical pharmacology perspective, although BE was established for all three active ingredients between the proposed drug product and the listed drugs (NDA 020204 Aleve and NDA 021620 Mucinex DM), the scientific bridge is only valid in the context that the proposed drug product follows a dosing regimen that is identical to that of the listed drug. The proposed dosing regimen of the proposed drug product (i.e., every 12-hour only) is different from the listed drug NDA Aleve, (i.e., every 8 to 12 hours). There is a concern that the efficacy of the naproxen component of the proposed drug product may not last the entire 12 hours. For more details, see the discussion in Section 6.3.1.

It is noted that the Applicant's BE assessment was based on plasma parent drug concentration for all three active ingredients. The draft guidance for industry *Bioequivalence Studies With Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA* (August 2021) indicates that the parent drug in the dosage form should always be measured in the biological fluids collected in BE studies. The guidance generally recommends that applicants measure only the parent drug, rather than metabolites, because the concentration-time profile of the parent drug is more sensitive to changes in formulation performance than a metabolite, which is more reflective of metabolite formation, distribution, and elimination. Primary metabolite(s), formed directly from the parent compound, should be measured if they qualify for both conditions: 1) are formed substantially through pre-systemic metabolism (gut wall or gut lumen metabolism), and 2) contribute significantly to the safety and/or efficacy of the product. Among three active ingredients in the proposed drug product, only dextromethorphan has an active metabolite, dextrorphan. However, given that dextrorphan is primarily metabolized by CYP2D6 after absorption into the systemic circulation, it is reasonable that the Applicant did not measure and compare the dextrorphan PK between the proposed drug product and the listed drug NDA 021620 Mucinex DM.

The Necessity and Adequacy of PBPK Modeling and Simulation Analysis

The Applicant's PBPK modeling and simulation analysis was considered inadequate to support the extrapolation of adult PK data to adolescents. The analysis was not sufficiently developed and verified for its intended purpose (refer to Section 14.5 for a full review).

However, based on the agreed initial pediatric study plan (dated May 2, 2019 under IND 105403), FDA agreed that no adolescent clinical PK studies were needed, and the adult PK data submitted can be used to extrapolate safety and effectiveness to pediatric subjects aged 12 to 17 years (adolescents). Of note, the listed drugs (NDA 020204 Aleve and NDA 021620 Mucinex DM) recommend the same dose and dosing regimen for adults and children of age of 12 years and above.

Conclusion

The pivotal PK Study RB5-US-1505 established BE of naproxen, guaifenesin, and dextromethorphan between the proposed drug product and the listed drugs (NDA 020204 Aleve and NDA 021620 Mucinex DM) at fasted state. The high fat meal has no apparent effect on systemic exposure of guaifenesin and naproxen for the proposed drug product. The food effect on dextromethorphan was similar between the proposed drug product and the listed drugs.

However, because the proposed dosing regimen (i.e., every 12-hour only) of the proposed drug product is different from the list drug NDA 020204 Aleve (i.e., every 8 to 12 hours); and there is a lack of direct PK comparison of naproxen between the proposed product and another listed drug NDA 021076, the scientific bridge to support the every-12-hour-only dosing regimen for the proposed drug product is incomplete.

6. Efficacy (Evaluation of Benefit)

6.1. Assessment of Dose and Potential Effectiveness

For the comparison of the dose and dosing regimen between the proposed product and listed drug products, refer to Table 6. For the discussion of different dosing frequency between the proposed product (i.e., every 12-hour only) and the listed drug NDA 020204 Aleve (i.e., every 8 to 12 hours), refer to Section 6.3.1.

6.2. Clinical Studies/Trials Intended to Demonstrate Efficacy

The Applicant conducted one pivotal PK study for the development of the proposed product and two pilot studies of prior formulations. Table 7 summarizes these studies.

Table 7. Listing of Clinical Studies

Study Identifier	Objective of Study	Study Design and Type of Control	Test Product(s)	Number of Enrolled Subjects	Healthy or Diagnosis of Subjects	Duration of Treatment
Pivotal clinical study						
RB5-US-1505	Relative bioavailability	Open label, randomized, balanced, four-treatment, four-period, crossover BA study of an experimental combination ER test product vs. co-administration of reference products under fasted and fed conditions	*Test product* • Two ER guaifenesin 600 mg/dextromethorphan HBr 30 mg/naproxen sodium 110 mg bilayer tablets *Reference product* • Co-administration of two Mucinex DM (guaifenesin 600 mg/dextromethorphan HBr 30 mg) tablets and one Aleve (naproxen sodium 220 mg) tablet	102	Healthy subjects	Single dose
Pilot clinical studies						
2009-GGE-TRI-DM	Relative bioavailability	Open label, randomized, balanced, four-treatment, four-period, crossover BA study of two experimental combination ER test products under fasted and fed conditions vs. co-administration of reference products under fasted conditions	*Treatment A* • (b) (4) formulation ER guaifenesin 600 mg/ dextromethorphan HBr 30 mg/naproxen sodium 220 mg bilayer tablet under fasted condition *Treatment B* • (b) (4) formulation ER guaifenesin 600 mg/ dextromethorphan HBr 30 mg/naproxen sodium 220 mg bilayer tablet under fasted condition *Treatment C* • (b) (4) formulation ER guaifenesin 600 mg/ dextromethorphan HBr 30 mg/naproxen sodium 220 mg bilayer tablet under fed condition *Reference product* • Co-administration of Mucinex (guaifenesin) 600 mg, Vicks Formula 44 Custom Care (dextromethorphan	30	Healthy subjects	Single dose

Study Identifier	Objective of Study	Study Design and Type of Control	Test Product(s)	Number of Enrolled Subjects	Healthy or Diagnosis of Subjects	Duration of Treatment
			HBr) 30 mg/15 mL syrup, and Aleve (naproxen sodium 220 mg)			
2014-MUCDM-NAP-02	Relative bioavailability	Open label, randomized, balanced, five-treatment, five-period, crossover BA study of two experimental combination ER test products vs. co-administration of reference products under fasted and fed conditions	*Treatment A* • Two capsules of (b) (4) formulation ER guaifenesin 600 mg/ dextromethorphan HBr 30 mg/naproxen sodium 110 mg bilayer tablet under fasted condition *Treatment B* • Two capsules of (b) (4) formulation ER guaifenesin 600 mg/ dextromethorphan HBr 30 mg/naproxen sodium 110 mg bilayer tablet under fed condition *Treatment C* • Two capsules of (b) (4) formulation ER guaifenesin 600 mg/ dextromethorphan HBr 30 mg/naproxen sodium 110 mg bilayer tablet under fasted condition *Treatment D* • Two capsules of (b) (4) formulation ER guaifenesin 600 mg/ dextromethorphan HBr 30 mg/naproxen sodium 110 mg bilayer tablet under fed condition *Reference product* • Co-administration of two Mucinex DM (guaifenesin 600 mg/dextromethorphan HBr 30 mg) tablets and one Aleve (naproxen sodium 220 mg) tablet under fasted condition	25	Healthy subjects	Single dose

Source: Generated by reviewer
Abbreviations: BA, bioavailability; DM, dextromethorphan; ER, extended-release; HBr, hydrobromide; mg, milligram; mL, milliliter; vs, versus

6.3. Key Efficacy Review Issues

6.3.1. Duration of Action Considerations and 12-Hour Dosing Regimen

Issue

The proposed product has dosing instructions to take two tablets every 12 hours. This dosing instruction for the naproxen component represents a modification from the dosing interval of the listed drug, Aleve, which has a dosing interval of every 8 to 12 hours and directions that allow for a loading dose of two tablets for the first dose. An additional product, Aleve-D Sinus and Cold, was added as a relied upon listed drug to establish an indirect bridge to justify the proposed 12-hour dosing for the naproxen component of the FDC product.

Background

This NDA was submitted pursuant to the 505(b)(2) regulatory pathway and initially only cross-referenced the Applicant's Mucinex DM (NDA 021620) and identified Aleve (NDA 020204) as the relied upon listed drug. When using the 505(b)(2) pathway, an applicant must establish that reliance on FDA's findings of safety and/or effectiveness for a listed drug is scientifically appropriate and must submit data necessary to support any aspect of the proposed drug product that represents modifications to each listed drug(s). To support this NDA, the Applicant proposed a scientific bridge that relied solely on demonstrating BE between its proposed product and each of the ingredients in Mucinex DM and Aleve and, reliance on previous FDA reviews to establish an indirect bridge to Aleve-D Sinus and Cold. The Applicant did not conduct an efficacy study. The clinical program of this NDA is discussed in Section 5.2.

The proposed dosing instruction differs from the dosing interval of one of the listed drugs (Aleve). The dosing instructions for this FDC product is to take two tablets (which provide 220 mg of naproxen sodium per dose) every 12 hours. Aleve has a dosing instruction to take one tablet (220 mg of naproxen sodium) every 8 to 12 hours with further directions to take two tablets (440 mg) as a first dose within the first hour, if needed (Table 6). In a June 5, 2023, Type B pre-NDA meeting, FDA raised the concern that consumers could lose analgesic and antipyretic efficacy of the naproxen component before the next dose was available to them. FDA advised the Applicant to provide data/information to support the proposed 12-hour dosing interval for the naproxen component. FDA also noted that "this may cause the need for consumer studies."

The Applicant provided the following justifications to support the 12-hour dosing interval of the FDC product (see Module 2.7.3 Summary of Clinical Efficacy, section 2.7.3.3):

- Naproxen sodium has a relatively long half-life of 12-17 hours, which allows for twice daily dosing intervals.
- Data from Aleve (NDA 020204) demonstrated that a "concentration of 15,000 ng/mL of naproxen sodium (at a 220 mg dose) was identified as the effective level for achieving a meaningful reduction in pain."

- FDA approved Aleve-D Sinus and Cold (naproxen sodium 220 mg/pseudoephedrine hydrochloride 120 mg, NDA 021076) for use every 12 hours.

In the filing letter dated December 11, 2023, FDA asked the Applicant to provide further data or information specific to support the fever indication for the entire 12-hour dosing interval for the proposed product. In a response dated December 28, 2023, the Applicant referred FDA to the NDA submission Module 2.7.3, section 2.7.3.3. The Applicant additionally noted that the 12-hour dosing interval and dosage for this FDC product is consistent with the previously approved Aleve-D Sinus and Cold (NDA 021076), which is indicated for temporary relief of fever. Of note, at that point, the Applicant did not identify NDA 021076 as a relied upon listed drug and no comparative PK study has been conducted to establish a direct scientific bridge between the proposed drug and NDA 021076.

In an Information Request letter dated March 22, 2024, FDA indicated to the Applicant that its justification that Aleve-D Sinus and Cold was approved with a dosing interval of 12 hours was insufficient. If the Applicant intended to rely on NDA 021076, then it would need to formally specify this reliance in its application and would need to provide adequate information to establish a bridge between its proposed drug and the relied-upon listed drug to demonstrate that such reliance is scientifically justified. The Applicant responded on April 12, 2024, with a revised Form FDA 356h that included Aleve-D Sinus and Cold as a relied upon listed drug and justifications to establish an indirect PK bridge.

Reviewers from DAAP, Division of Neuropsychiatric Pharmacology, Office of New Drug Policy were consulted to evaluate this issue.

Assessment

The Applicant has provided three justifications to support the difference in dosing instruction between its proposed product and its listed drug, Aleve.

- The first argument is that naproxen has a relatively long half-life of 12-17 hours, which the Applicant asserts should allow for twice daily dosing intervals. To support this, the Applicant cited an article by Capone et al. 2007. The study was conducted using an ex vivo and in vitro approach in six healthy subjects who received naproxen sodium (220 and 440 mg b.i.d.) and aspirin (100 mg daily) for 6 days, separated by washout periods of 2 weeks. Blood samples were collected before dosing and on the sixth day after the last dose of the different treatments (at 1, 2, 5, 8, 12, and 24 hours after dosing) to assess naproxen concentrations, the inhibition of serum thromboxane B2 (a capacity index of platelet cyclooxygenase-1 [COX-1] activity), lipopolysaccharide-induced prostaglandin E2 production (a capacity index of monocyte COX-2 activity), and platelet aggregation induced by 2mM arachidonic acid in platelet-rich plasma. The authors observed that naproxen sodium at 220 mg showed notable inhibition of COX-1 enzymes and platelet aggregation at the 12- and 24-hour marks and achieved approximately 80% inhibitory concentration for COX-2 enzyme activity at 12 hours. Based on this study, the Applicant concluded that naproxen's sustained inhibitory effects on enzymes and inflammatory mediators could result in sustained analgesic and anti-inflammatory effects.

Although the half-life of naproxen is observed to be 12-17 hours, the dosing directions established for nonprescription naproxen use was approved based on clinical efficacy data generated for NDA 020204. Additionally, as noted in Dr. Srikanth C. Nallani's (DAAP clinical

pharmacology) consult (May 2, 2024, DARRTS Reference ID 5374474), the observations in the Capone publication were very limited and did not employ proper PK/pharmacodynamic (PD) methodology to associate the relationship between plasma naproxen concentration and PD activity pertinent to clinically impactful analgesia or antipyresis. Please see Dr. Nallani's consult memorandum for more details.

- The Applicant's second argument is that the data from the approval package for NDA 020204 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." The Applicant asserts that the naproxen component of its proposed product maintains efficacy throughout the proposed 12 hours dosing interval because the naproxen plasma concentrations from its proposed product in both fasted and fed conditions achieved the 15,000 ng/mL level for the entire duration. Thus, the Applicant believes the naproxen component of this FDC product maintains efficacy throughout the entire dosing period up to 12 hours.

Dr. Timothy Jiang's (DAAP clinical) consult (May 21, 2024, DARRTS Reference ID 5383829) summarized relevant information from the approval package for NDA 020204. The original discussion of a 15,000 ng/mL concentration level for naproxen was based on observations from Study LAB693. LAB693 was a placebo-controlled PK/PD molar extraction study. According to the 1994 biopharmaceutics review by E. Dennis Bashaw,[4] LAB693 evaluated naproxen (b) (4) mg (b) (4) tablet instead of the final to-be-marketed dosage form (i.e., naproxen sodium 220-mg tablet). The study had four arms with a total of 103 subjects enrolled and 82 completers; thus, the sample size was small per treatment arm. Pain scores were recorded at various timepoints up to 8 hours postdose. One observation was that to achieve a pain intensity difference reduction of 1 unit on a 4-point pain scale, the plasma concentration of naproxen must exceed ~15,000 ng/mL or greater. However, the study did not reveal a separation of pain intensity difference between the placebo and study drug, nor PK dose proportionality until 2 hours postdose. Additionally, the study was notable for many flaws in its design and analysis including insufficient plasma sampling and PD measurements during the absorption phase, the use of C_{max} and AUC alone for determining BE, which was inappropriate in situations where shifts in other PK parameters could affect clinical outcomes, and the lack of additional analytical techniques to evaluate the absorption phase.

The DAAP team disagrees with the Applicant that a plasma concentration of 15,000 ng/mL is the effective concentration for naproxen sodium. LAB693 was designed as a dose-finding study to guide formulation development for the to-be-marketed Aleve 220-mg tablets and not for substantial evidence of effectiveness for NDA 020204. Efficacy data to support approval of NDA 020204 came from 34 other studies demonstrating efficacy of Aleve 220-mg tablet, not Study LAB693. Furthermore, both Drs. Jiang and Nallani pointed out that the Applicant's utilization of plasma concentrations noted in a small study from another NDA is not valid without utilizing proper methodology. Plasma concentrations across different studies may be different because of differences in the timing of plasma and PD assessments as well as differences in subject ages, bodyweight, race, sex, and ethnicity. They conclude that from a scientific perspective, the Applicant's PK/PD assertion that a concentration of 15,000 ng/mL of naproxen was the effective level for achieving a meaningful reduction in pain is not valid.

[4] E. Dennis Bashaw, 1994, Biopharmaceutics Review, NDA 020204 Action Package, pages 27 to 35.

Additionally, from a regulatory perspective, the Applicant's use of the summary basis of approval for the listed drug Aleve is not an acceptable source of information that may be used in support of a 505(b)(2) NDA. A 505(b)(2) applicant may rely upon FDA's previous finding of safety and effectiveness for a listed drug as reflected in the FDA-approved labeling for the listed drug. Additional details are available in Drs. Jiang (Review dated May 21, 2024, DARRTS Reference ID 5383829) and Nallani's (Review dated May 2, 2024, DARRTS Reference ID 5374474) consult memoranda.

- The Applicant's third argument is that the relied upon listed drug, Aleve-D Sinus and Cold (NDA 021076), was approved as a naproxen-containing combination product for a similar indication of use and with directions of use for every 12-hours. NDA 021076 contains clinical efficacy data, which supported the 12-hour dosing interval of Aleve-D Sinus and Cold. Two pivotal trials were conducted using a cold model to support its approved uses and directions. The Applicant has provided rationale to establish an indirect PK bridge based on published literature and cross study comparison of PK data retrieved from FDA's review of NDA 021076 in the IR response dated April 12, 2024.
    - The Applicant noted that the combination of active ingredients in the proposed drug product is different than that of Aleve-D Sinus and Cold; however, they claimed that regardless of the differences in combinations, the 12-hour regimen can be applied to the proposed drug product because:
        - Naproxen sodium is completely absorbed, and
        - Naproxen's PK profile is independent of combination pharmaceutical products, formats, or co-administration.

    To support this argument, the Applicant cited three scientific publications; Choi et al. 2015, Palma-Aguirre et al. 2009, and Toothaker et al. 2000.

There is no sufficient evidence to show that the in vivo performance of solid oral dosage forms of naproxen sodium will not be affected by formulation strategy. It is common knowledge that the oral BA of an active ingredient could be affected by formulation, and thus, is drug product/formulation specific. Therefore, establishing BE (based on PK parameters such as AUC and C_{max}) is required to provide the regulatorily needed scientific bridge between the proposed naproxen sodium product and the relied upon listed drug. In addition, there are no existing published data on the absolute BA of naproxen as determined via a well-designed mass balanced study. The articles that the Applicant cited included data from in vivo studies conducted with different combinations of naproxen and other active ingredients in the context of different formulations when compared to the formulation of the proposed drug product.

- Choi et al. 2015 conducted an in vivo BE study to compare two products containing a combination of naproxen and esomeprazole.
- Palma-Aguirre et al. 2009 assessed the BA of two oral-tablet and two oral-suspension formulations of naproxen sodium/paracetamol (acetaminophen).

Findings from these studies cannot be generalized to establish an indirect bridge between the proposed drug product and Aleve-D Sinus and Cold. In addition, it is unclear whether any of the studied products in these two papers have been approved by FDA.

Toothaker et al. 2000 studied the mutual impact on systemic exposure of naproxen and diphenhydramine when these active ingredients are co-administered. The outcome from this study is also not applicable to bridge the proposed product and Aleve-D Sinus and Cold given the context of different formulations used when compared to the formulation of the proposed drug product.

- In its response to Information Request dated April 12, 2024, the Applicant proposed an indirect scientific bridge, which relied on BE conclusion from the clinical pharmacology review (CDER 1999) for NDA 021076 Aleve-D Sinus and Cold, which was demonstrated between Aleve-D Sinus and Cold and Aleve in Study S98-068; and the BE between the proposed drug product and Aleve established from Study RB5-US-1505 in this NDA.

This approach is not acceptable as FDA reviews are not considered an appropriate source of information to rely on for approval from a regulatory perspective. FDA's publicly available reviews do not constitute "full reports of investigations" of safety and effectiveness required to be submitted for approval of 505(b)(1) and 505(b)(2) NDAs (see 21 C.F.R. 314.430(e)(2)). Thus, the Applicant's response to support the scientific bridging between the proposed drug and Aleve-D Sinus and Cold is considered inadequate.

Naproxen sodium is reported as a biopharmaceutics classification system class II drug, which means that this drug has a high permeability and poor solubility (Takagi et al. 2006; Allesø et al. 2009; Ying et al. 2014). Naproxen sodium is soluble in water at pH of 7.4, sparingly soluble at pH of 6, 8, and 4.5, and very sparingly soluble at pH 1.2 (Lalit Kumar et al. 2015; Larisa Alagić-Džambić et al. 2020). Thus, as an active ingredient, naproxen sodium does not qualify for a biowaiver based on M9 biopharmaceutics classification system-based biowaiver (May 2021). The Office of Generic Drugs recommends conducting in vivo BE studies in fed and fasted condition for generic applicants seeking to develop a generic product referencing Aleve-D Sinus and Cold (February 2018). Thus, the same approach is appropriate for this Applicant if they seek to establish a direct scientific bridge between the proposed drug product and Aleve-D Sinus and Cold. A regulatorily acceptable way for the Applicant to support this scientific bridge is to establish BE directly between the proposed drug product and Aleve-D Sinus and Cold in a two-way crossover in vivo BE study.

Conclusion

The Applicant has not provided sufficient data supporting the proposed 12-hours-only dosing regimen of the naproxen sodium component of the proposed product. Demonstration of BE to the listed Aleve tablets alone is not adequate to support the proposed dosing interval. The Applicant has not identified an appropriate source of data or information that can be relied upon from a scientific or regulatory perspective, nor has it obtained a right of reference to adequate data support to approval of the proposed product.

7. Safety (Risk and Risk Management)

7.1. Potential Risks or Safety Concerns Based on Nonclinical Data

No new or original nonclinical data were requested or submitted to support safety of the active ingredients in this NDA. The Applicant is relying upon FDA's findings of safety for previously approved drugs that contain the proposed active ingredients.

The Pharmacology/Toxicology reviewer conducted a safety assessment of the proposed excipients in the proposed formulation. The proposed formulation does not contain any novel excipients. The proposed excipients are supported by their use in approved drug products identified in the FDA internal Inactive Ingredient Report database with similar clinical conditions of use (i.e., maximum daily exposure, route of administration, patient population, duration of use), and/or by a supportive food additive regulation published in the CFR. The only excipient that was not reviewed by the Pharmacology/Toxicology reviewer is the colorant, Food, Drug and Cosmetics Red. Refer to the chemistry, manufacturing, and controls/Office of Pharmaceutical Quality (OPQ) review (Dated May 29, 2024, DARRTS Reference ID 5388953) for comments on compliance of the proposed use of Food, Drug and Cosmetics Red with Center for Food Safety and Applied Nutrition Color Additive regulations. Refer to Table 8 which provides the proposed formulation and the information relied upon by the Pharmacology/Toxicology reviewer to support the safety of the proposed excipients for the proposed clinical conditions of use.

Table 8. Proposed Inactive Ingredients and Information To Support Use

Component	CAS	Per Tablet Amount (mg/tablet)[1]	Total MDE Upper Bound (mg)[2]	Supportive 21 CFR Listing	Inactive Ingredient Report Support (Y/N/NF)[3]
Sodium lauryl sulfate	151-21-3	(b) (4)		172.88	Y
Sodium bicarbonate	144-55-8			184.1736	Y
Polyethylene glycol	25322-68-8			172.820	Y
Microcrystalline cellulose	977005-28-9			Not found	Y
Croscarmellose sodium	74811-65-7			Not found	Y
Hypromellose	9004-65-3			172.874	Y
Hydroxyethyl cellulose	9004-62-0			Not found	Y
Magnesium stearate	557-04-0			184.1440	Y
FD&C Red*					

Source: Reviewer Generated
[1]Level of each excipient reported by the Applicant in the NDA submission, 3.2.P.1.2.1 Unit Dose Composition
[2] Maximum daily exposure of each excipient which considers the maximum recommended clinical dose of the drug product (4 tablets) and the amount of each excipient in each tablet.
[3]Yes, No, or Not found: This description refers to the availability of NDAs or ANDAs in the Internal Inactive Ingredient Report which support the proposed clinical context of use (maximum daily exposure, duration, patient population, route of exposure) for each excipient.
*The regulatory compliance of the proposed use this colorant with Center for Food Safety and Applied Nutrition Color Additive regulations is the purview of CMC/OPQ.
Abbreviations: CAS, Chemical Abstracts Service; CFR, Code of Federal Regulations; FD&C, Food, Drug, & Cosmetics; MDE, maximum daily exposure; mg, milligram; Y/N/NF, yes, no, or not found

7.2. Potential Risks or Safety Concerns Based on Drug Class or Other Drug-Specific Factors

There are no approved commercial products that contain a combination of guaifenesin, dextromethorphan, and naproxen in the United States. Nevertheless, all three ingredients in this proposed FDC product have been widely used in the nonprescription setting and have a well-established safety profile as single component products as well as some combination products (see Section 3). Additionally, given that there is no known interaction among the three ingredients as per approved labeling, and the metabolic pathways for the ingredients are different, the potential risks of this FDC product are expected to align with those of the individual components.

Use of guaifenesin is associated with the following adverse reactions: dizziness, drowsiness, headache, skin rash, hyperuricemia, nausea, stomach pain, vomiting, and rarely, nephrolithiasis with consumption of large quantities (Lexicomp 2024b).

Use of dextromethorphan is associated with the following adverse reactions: dizziness, drowsiness, nervousness, restlessness, gastrointestinal (GI) distress, nausea, stomach pain, and vomiting. Concurrent administration of dextromethorphan with, or within two weeks of discontinuing a monoamine oxidase inhibitor is a contraindication. Serotonin syndrome may occur with concomitant administration of dextromethorphan with proserotonergic drugs (i.e., selective serotonin reuptake inhibitors/serotonin and selective norepinephrine reuptake inhibitors, or triptans), especially with higher dextromethorphan doses. The following special populations need to use dextromethorphan with caution:

- CYP2D6 poor metabolizers may have an exaggerated or prolonged effect of dextromethorphan. Increased risk of this may be seen with concomitant use of potent CYP2D6 inhibitors.
- Sedated, debilitated patients, or those confined to a supine position.

Dextromethorphan is associated with problems of abuse or misuse. Overdose can cause death, brain damage, seizure, loss of consciousness, and/or irregular heartbeat.

Patients with underlying medical conditions associated with a persistent or chronic cough such as that occurs with asthma, chronic obstructive pulmonary disease, emphysema, or smoking, or cough associated with excessive mucous production should consult with a health care provider prior to the use of guaifenesin and/or dextromethorphan (Lexicomp 2024a).

Use of naproxen and other nonsteroidal anti-inflammatory drugs (NSAIDs) is associated with an increased risk of GI adverse effects. The risk of serious GI complications increases with increased duration of therapy and higher doses. NSAIDS are also associated with serious skin reactions, hypersensitivity reactions with anaphylaxis particularly in those with asthma, occurrence or worsening of kidney injury, particularly when combined with other potentially nephrotoxic agents, increased risk of adverse cardiovascular (CV) thromboembolic events, including myocardial infarction, and stroke. This CV risk varies based on the NSAID chosen, the dose used, the duration of use, and an individual's baseline CV risk factors. Additionally,

NSAIDs are associated with attenuation of aspirin's antithrombotic effects on platelets, if administered before aspirin.

7.3. Potential Risks or Safety Concerns Identified Through Postmarket Experience

As noted, no approved commercial products contain a combination of guaifenesin, dextromethorphan, and naproxen in the United States or any other country. However, analyses of postmarketing safety data for the concomitant use of these ingredients are presented in Section 7.6.2.1.

7.4. FDA Approach to the Safety Review

The clinical safety of the three active ingredients in the proposed FDC product has been well established given each ingredient's longstanding use in the nonprescription setting.

The main consideration for this safety review is whether the proposed FDC product can be used safely in the nonprescription setting. The systemic safety of each of the active ingredients is supported by its PK data demonstrating BE with the listed drugs. Safety of the concomitant use of these ingredients will rely on safety data generated from the PK studies. The clinical safety data generated from Pivotal PK Study RB5-US-1505 is reviewed in Section 7.6.1.

To further support safety of the proposed product, the Applicant conducted a review of postmarketing safety data as well as published literature focusing on adverse events (AEs) associated with the concomitant use of the three active ingredients. The primary value of these evaluations was to identify unexpected or serious events not previously recognized for guaifenesin, dextromethorphan, and naproxen products. The Applicant's evaluation utilized several postmarket safety databases including:

- The Applicant's internal pharmacovigilance database
- FAERS
- WHO Vigibase
- NPDS
- Literature review

The postmarketing safety data are reviewed in Section 7.6.2.

Additionally, the CSS was consulted to evaluate the abuse and misuse potential of the proposed product since dextromethorphan is a known ingredient of abuse. A summary of this consult is provided in Section 7.7.3. For a full review, please refer to the CSS review dated January 22, 2024 (DARRTS Reference ID:5314327).

7.5. Adequacy of the Clinical Safety Database

One hundred and two subjects were enrolled in pivotal Study RB5-US-1505. Of these, 71 subjects received two doses of the proposed product, and 23 subjects received one dose. Study RB5-US-1505 used the intend-to-market formulation. Considering each of the ingredients' well-established safety profile and extensive postmarketing experience, the safety database generated from the PK study is adequate.

For the purpose of this nonprescription application, the safety database also included the Applicant's evaluation of postmarketing safety data and published literature for safety issues related to the independent and concomitant nonprescription use of the three active ingredients. These evaluations were conducted according to expectations for a nonprescription application and are considered adequate to support the review.

7.6. Safety Results

FDA defines an AE as any untoward medical occurrence associated with the use of a drug in humans, whether it was considered drug-related or not. Therefore, an AE can be any unfavorable and unintended sign, symptom, or disease temporally associated with use of a drug product. The categorization of AE from the clinical developmental program is acceptable. AEs were attributed to the most recent treatment received prior to the AE. Treatment-emergent adverse events (TEAEs) were defined as any AEs not present before exposure to study drug or any event already present that worsened in intensity or frequency after exposure. Case reports categorized as having serious outcomes are defined as having any adverse drug event that results in death, a life-threatening event, hospitalization, disability or permanent damage, congenital anomaly or birth defect, requirement of an intervention to prevent permanent impairment or damage, or other serious important medical events.

In the pivotal PK study, investigators were required to report all directly observed AEs and all AEs spontaneously reported by study subjects. Study subjects were questioned about AEs at all post-baseline assessments. The investigator made severity assessments and causality assessments for all AEs. The terms "mild," "moderate," and "severe" were used to describe the severity of an AE using the definitions in Table 9.

Table 9. Definitions for Adverse Event Severity

Adverse Event Severity	Definition
Mild	AE does not limit usual activities; the subject may experience slight discomfort
Moderate	AE results in some limitation of usual activities; the subject may experience significant discomfort
Severe	AE results in an inability to carry out usual activities; the subject may experience intolerable discomfort or pain

Source: Adapted from eCTD Module 5.3.1.1 Study Report Body
Abbreviation: AE, adverse event

The causality assessment determined if there is a reasonable possibility that the investigational product caused or contributed to an AE. The investigator determined this relationship using the definitions in Table 10.

Table 10. Definitions for Adverse Event Causality

Relationship	Description
Unrelated	No possibility that the AE was caused by the test product
Unlikely	Slight, but remote, chance that the AE was caused by the test product, but the balance of judgment is that it was most likely not due to the test product
Possible	Reasonable suspicion that the AE was caused by the test product
Probable	Most likely that the AE was caused by the test product
Certain	The AE was definitely caused by the test product

Source: Adapted from eCTD Module 5.3.1.1 Study Report Body
Abbreviation: AE, adverse event

Coding of AEs and medical history was done using the Medical Dictionary for Regulatory Activities version 25.1.

7.6.1. Clinical Safety Results

7.6.1.1. Study RB5-US-1505

Overview and Objectives

RB5-US-1505 was an open-label, randomized, balanced, single-dose, four-treatment, four-period, crossover relative BA study of an experimental combination ER formulation of guaifenesin 600 mg, dextromethorphan HBr 30 mg, and naproxen sodium 110 mg bilayer tablets (test product, (b) (4)) compared to a co-administration of Mucinex DM and Aleve tablets (reference product) under fasted and fed conditions.

The primary objective of this study was to assess the relative BA of each of the three active ingredients from the test product and the listed drugs Mucinex DM and Aleve when co-administered in healthy adults in the fasted state.

The secondary objectives of this study were to:

- Assess the safety and tolerability of test product and reference product combination in healthy adults.
- Assess and compare the food effect from the test product and reference product combination.
- Assess the relative BA of each of the three active ingredients from the test product and reference product combination under fed conditions.

Methodology

The study consisted of a pre-study screening visit followed by four treatment periods. Each of the treatment periods were 6 days in duration (Day 1 to Day 5).

Subjects who met the inclusion and exclusion criteria were assessed for final eligibility and admitted to the Clinical Unit. Subjects were randomized to receive one of four treatments (A, B, C, or D) in accordance with the randomization schedule. The treatments for each period included:

- A: Two (b) (4) tablets after an overnight fast of 10-hours

- B: Two (b) (4) tablets after a high-fat meal, preceded by an overnight fast of 10 hours
- C: Two Mucinex DM tablets co-administered with one Aleve tablet after an overnight fast of 10 hours
- D: Two Mucinex DM tablets co-administered with one Aleve tablet after one Aleve tablet after a high-fat meal, preceded by an overnight fast of 10 hours

During the study, blood samples were collected at various time points to measure the concentration of guaifenesin, dextromethorphan, and naproxen in the participants' plasma. AEs were solicited at 6-, 12-, and 24-hours postdose and spontaneously reported AEs and concomitant medications were recorded.

There was a minimum washout of 10 days between drug administrations in each period.

AEs, vital signs, electrocardiogram, physical exam, routine laboratory tests (hematology, biochemistry, urine drug screen, pregnancy (if applicable), and CYP2D6 metabolizer status were measured as safety endpoints.

Demographics

Most subjects were White (84/102; 82.35%); thirteen subjects were Black or African American (13/102; 12.75%); two subjects were Asian (2/102;1.96%); Six subjects were Hispanic or Latino (6/102; 5.88%); Fifty-three subjects were male (53/102; 51.96%); forty-nine subjects were female (49/10; 48.04%). Subjects' ages ranged from 16-55 years.

Safety Results

One hundred and two subjects were randomized and received at least one dose of the study drug. These subjects were included in the safety analyses. Sixty-one subjects completed all study treatments and forty-one subjects discontinued from the study prematurely (see below). Overall, 53 subjects (53/102; 51.96%) reported a total of 107 TEAEs. There were no deaths or serious adverse events in this study.

The Applicant reported one hundred and six (106/107; 99.1%) TEAEs considered mild in severity and one (1/107; 0.9%) TEAE (headache) considered moderate in severity. The TEAEs were evenly distributed across the four treatment periods.

Table 11. TEAEs and Severity by Treatment Group

TEAEs and Severity	Total (N=102)	Treatment A (N=83)	Treatment B (N=82)	Treatment C (N=79)	Treatment D (N=76)
Number of subjects reporting AE (%)	53	22 (26.51%)	14 (17.07%)	17 (21.52%)	21 (27.63%)
TEAE- All causality	107	31	26	23	27
Severity					
Mild	52	21	14	17	21
Moderate	1	1	0	0	0
Severe	0	0	0	0	0

Source: Table generated by reviewer. Adapted from data in eCTD, Module 5.3.1.1 Study RB5-US-1505
Abbreviations: AE, adverse event; N, number (of population) TEAE, treatment-emergent adverse event

The most frequently reported TEAEs in greater than 2% of subjects are coronavirus disease 2019 (COVID-19) infection (16/102; 15.69%), dizziness (16/102; 15.69 %), and headache (15/102; 14.71%) followed by a variety of GI symptoms, back pain, diarrhea, and fatigue. These AEs occurred relatively evenly across treatment groups, i.e., they appeared with similar frequency in both test (Treatments A and B) and reference arms (Treatments C and D).

Table 12. Most Frequently Reported TEAEs (>2% of Subjects) by Treatment Group

Preferred Term	Total (N=102)	Treatment A (N=83)	Treatment B (N=82)	Treatment C (N=79)	Treatment D (N=76)
COVID-19 infection	16 (15.69%)	6	2	3	5
Dizziness	16 (15.69%)	3	5	4	4
Headache	15 (14.71%)	6	5	2	6
Nausea	4 (3.92%)	1	3	1	2
Vomiting	4 (3.92%)	1	1	1	1
Abdominal pain	3 (2.94%)	2	0	1	0
Back Pain	3 (2.94 %)	2	0	3	0
Diarrhea	3 (2.94%)	2	0	3	0
Fatigue	3 (2.94%)	1	1	0	1

Source: Table generated by reviewer. Adapted from data in eCTD, Module 5.3.1.1 Study RB5-US-1505
Abbreviations: COVID-19, coronavirus disease 2019; N, number of population; TEAE, treatment-emergent adverse event

The majority of TEAEs were resolved by end of study (103/107; 96.3%). One TEAE was noted as being “resolved with sequelae” that were not otherwise specified; however, it was noted after taking the reference product. The resolution of three TEAEs is unknown since the subject was lost to follow up. These three TEAEs were noted after taking the study drug and all were considered mild in severity.

Discontinuations

Forty-one subjects (41/102; 40.2%) did not complete the study. Sixteen of the discontinued subjects (16/41; 39%) were discontinued secondary to COVID-19 infection. Fourteen of the discontinued subjects (14/41; 34.2%) reported an AE and were discontinued for the following reasons: 1) six subjects (6/41;14.6%) were discontinued due to their reported AE; 2) six subjects (6/41; 14.6%) were discontinued by the investigator for a drop in their hemoglobin level of more than 2 gm/dL, or had a hemoglobin <11 gm /dL thought to be caused by the previous blood draw that was performed for this study as per the protocol exclusion criteria; 3) two subjects (2/41;4.9%) reportedly discontinued due to personal reasons though AEs were noted, including cold symptoms and headache in one subject and headache in the second subject. Of the eleven remaining discontinued subjects (11/41; 26.8%), none reported AEs; however, four reported discontinuation for self-reported personal reasons, five were disqualified by the investigator, and two were lost to follow up. Each discontinuation and reason is reviewed in Table 13.

Table 13. Subject Discontinuation and Reasons for Discontinuation

Number of Subjects Who Discontinued (N=41)	Reason for Discontinuation Provided by Applicant/AE Status	Case Report
16	• COVID-19 infection	
6	• Adverse Event	• **Subject** (b) (6)**:** Discontinued for AE of fever. AE pyrexia not related to drug product. Resolved. • **Subject** (b) (6)**:** Discontinued for AEs of high white blood cells, lymphocytes. AE not related to drug product. Resolved. • **Subject** (b) (6)**:** Discontinued for AEs of heartburn, fatigue, dizziness, cold sweats, shortness of breath, light headedness. Resolved. • **Subject** (b) (6)**:** HBP, mild light headedness, "bubbles in chest." Discontinued for elevated HBP. HBP occurred 14 days after drug product. AE most likely not related to effect caused by drug product. Resolved. • **Subject** (b) (6)**:** Discontinued for AE. Reported AEs stomach pain, vomit, bilateral leg pain. Resolved. • **Subject** (b) (6)**:** Discontinued for AE. HA, moderate.
6	• Discontinued by PI per protocol for "Safety Reason" decrease in Hgb >2gm/dL (compared to screening Hgb) or below 11 gm/dL • AE reported	• **Subject:** (b) (6)**:** Discontinued from the study due to drop in Hgb level of 2.4 gm/dL (>2 gm/dL) per protocol exclusion criteria. AE reported – "sore back." • **Subject** (b) (6)**:** Discontinued from the study due to drop in Hgb level of 2.3 gm/dL per protocol exclusion criteria. AE reported – "feeling faint." • **Subject** (b) (6)**:** Discontinued from the study due to Hgb level being < 11gm/dL per protocol exclusion criteria. AEs reported- "HA," "foggy head," "neck stiffness." • **Subject 0** (b) (6)**:** Discontinued from the study due to drop in Hgb level of 2.1 gm/dL per protocol exclusion criteria. AEs reported, "lightheaded," "abdominal cramps." • **Subject** (b) (6)**:** Discontinued from the study due to Hgb level being < 11gm/dL per protocol exclusion criteria. AE reported, urinary tract infection. • **Subject** (b) (6)**:** Discontinued from the study due to Hgb level being < 11gm/dL per protocol exclusion criteria. AE reported, "lightheaded."
2	• Personal reasons • AE reported	• **Subject** (b) (6)**:** "Personal reason." AEs reported, "cold symptoms" and "HA." HA resolved without intervention. • **Subject** (b) (6)**:** "Personal." AE reported, "HA." HA resolved without intervention.

Number of Subjects Who Discontinued (N=41)	Reason for Discontinuation Provided by Applicant/AE Status	Case Report
2	• Discontinued by PI per protocol for "Safety Reason" decrease in Hgb >2gm/dL (compared to screening Hgb) or below 11 gm/dL • No AE Reported	• **Subject** (b) (6)**:** Discontinued from the study due to Hgb level being < 11gm/dL per protocol exclusion criteria. No AE reported. • **Subject** (b) (6)**:** Discontinued from the study due to drop in Hgb level of 2.1 gm/dL per protocol exclusion criteria. No AE reported.
9	• "Personal," "personal reason(s)," disqualified or lost to follow-up • No AE reported	• **Subject** **:** Lost to follow-up. No AE reported. • **Subject** **:** Lost to follow-up. No AE reported. • **Subject** **:** Positive drugs of abuse. No AE reported. • **Subject** **:** "Personal reason." No AE reported. • **Subject** (b) (6)**:** "Personal reason." No AE reported. • **Subject** (b) (6)**:** "Personal." No AE reported. • **Subject** (b) (6)**:** "Personal." No AE reported. • **Subject** (b) (6)**:** Discontinued for "noncompliance that affects data integrity." No AE reported. • **Subject** (b) (6)**:** COVID-19 exposure. No AE reported.

Source: Table generated by reviewer. Adapted from data in eCTD, Module 5.3.1.1 Study RB5-US-1505 and from Applicant's Response to Information Request, submitted November 27, 2023.
Abbreviations: AE, adverse event; COVID-19, coronavirus disease 2019; dL, deciliter; gm, gram; HA, headache; HBP, high blood pressure; Hgb, hemoglobin; N, number (of population); PI, Prescribing Information

The majority of the discontinuations were not due to AEs from the investigational products. Based on review of the case reports and the AEs, the majority of discontinuations were related to COVID-19 infections and nonstudy-related personal issues or disqualifications due to protocol violations. Of the six discontinuations that were due to an AE, the Applicant's assessments that the discontinuations were not caused by the investigational product were considered reasonable.

Laboratory Findings

Laboratory evaluations were performed for screening purposes. A single subject had a laboratory finding that was reported as a TEAE. The subject was found to have elevated white blood cell count after receiving Treatment D. The subject was discontinued from the study.

Vital Signs

Vital signs including blood pressure, heart rate, respiratory rate, and temperature were collected at baseline and end of study. A single subject experienced a vital sign abnormality that was reported as a TEAE. The subject was noted to have elevated blood pressure up to 162/93 after receiving Treatment A. The TEAE was considered to be mild in intensity per the investigator. The subject was discontinued from the study. The hypertension eventually resolved on follow-up. No other clinically significant vital sign changes were measured during the study.

Electrocardiograms

An electrocardiogram was collected at baseline and eight hours after study treatment for all subjects. The Applicant reported no clinically significant abnormal electrocardiogram results during the study.

No clinically significant abnormalities in physical examinations were observed during the study.

7.6.2. Adverse Events Identified in Postmarket Experiences

All postmarketing safety databases are susceptible to inherent limitations, including but not limited to: under-reporting, a lack of reporting standards, incomplete reporting, duplication, reporter bias, and the presence of potential confounding factors within a case that preclude a causal assessment. Many factors can influence whether or not an event will be reported, such as the amount of time a product has been marketed and publicity about an event. Additionally, there is no way to know the true denominator of patient exposure or the true number of cases for any AE. Therefore, pharmacovigilance safety data cannot be used to calculate the incidence of an AE event or medication error in the U.S. population. Although these issues limit our ability to draw definitive conclusions based on the postmarketing experience, analyses of this information can provide some useful insights as to the potential unexpected or serious events not previously recognized for the three active ingredients- guaifenesin, dextromethorphan, and naproxen as single ingredients or in combination. This review could additionally give insight into the AEs that might represent issues for the proposed combination product and could inform its labeling.

7.6.2.1. Summary of Applicant's Postmarketing Safety Analysis

For this NDA, the Applicant provided an analysis of domestic and foreign postmarketing safety data for guaifenesin, dextromethorphan, and naproxen when used concomitantly as well as when used as single ingredients. Pharmacovigilance data sources included the company's pharmacovigilance database, FAERS, WHO Vigibase, and the NPDS. To highlight the most helpful and relevant information in consideration of this FDC product, this review focuses on AEs that occurred in cases reporting concomitant use of the three active ingredients in this product.

7.6.2.1.1. Postmarket Safety Evaluation From the Applicant's Pharmacovigilance Database

The Applicant conducted a search of cases reporting AEs associated with concomitant use of guaifenesin, dextromethorphan, and naproxen in its company pharmacovigilance database. Initially, this request covered a 5-year period from July 1, 2018, to June 30, 2023, but was later extended to include the past 10-year period from July 1, 2013, to June 30, 2023 due to low numbers of reported cases. Medical Dictionary for Regulatory Activities version 26.1 was used to code AEs from this search.

During the 10-year period from July 1, 2013, to June 30, 2023, RB Health identified a total of six cases that reported concomitant use of the three active ingredients. Four of these cases were reported in males and two in females. Of the cases wherein age was known, two occurred in individuals 18 to < 65 years of age, and two occurred in individuals older than 65 years of age. Ages were unknown in two of the reported cases. None of the cases occurred in those less than 18 years of age.

No deaths or serious cases were identified within the Applicant's pharmacovigilance database. All six cases were considered nonserious. The most frequently appearing preferred term (PT) among all six cases was insomnia, which was reported twice. Table 14 provides system organ classes and PT for all six cases.

Table 14. RB Health Safety Database Cases Reporting Concomitant Use of Guaifenesin, Dextromethorphan, and Naproxen (SOC/PT)

Dextromethorphan + Guaifenesin + Naproxen (01-Jul-13 to 30-Jun-23)		
System Organ Class	**Preferred Term**	**Count of Preferred Term**
Ear and labyrinth disorders	Tinnitus	1
Gastrointestinal disorders	Abdominal pain lower	1
General disorders and administration site conditions	Gait disturbance	1
Injury, poisoning and procedural complications	Fall	1
	Inappropriate schedule of product administration	1
	Incorrect dose administered	1
Nervous system disorders	Headache	1
	Somnolence	1
Psychiatric disorders	Insomnia	2
	Restlessness	1
Vascular disorders	Hypertension	1

Source: RB Health Response to Information Request submitted January 9, 2024, Table 9, page 21.
Abbreviations: Jul, July; Jun, June; PT, preferred term; SOC, system organ class

Overall, considering the wide use of nonprescription analgesics/antipyretic, cough and cold preparations including guaifenesin, dextromethorphan, and naproxen, it is reassuring that the total number of concomitant cases reported were very small, and all were considered nonserious.

7.6.2.1.2. FDA Adverse Event Reporting System

The Applicant's analysis of cases associated with concomitant use of the three active ingredients covered a 10-year period from July 1, 2013, to June 30, 2023. The Applicant identified a total of 45 cases in FAERS. Of the cases wherein age was reported, five (5/45; 11.1%) involved adolescents ages 12 to less than 18 years, and a majority of 27 cases (27/45; 60%) involved adults greater than 18 years. No cases involved individuals less than 12 years. When [redacted] was reported, the majority of cases involved females (25/45; 55.6%) compared with males (14/45; 31.1%).

Of the 45 cases associated with concomitant use of the three active ingredients, 16 cases (16/45; 35.6%) were assessed as serious. The patient characteristics including age, [redacted] and seriousness for all cases can be found in Table 15.

Table 15. FAERS Patient Characteristics Cases Involving Concomitant Use of Three Active Ingredients

[redacted]	<12 years		12 - <18 years		18- <65 years		65 + years		Unknown Age	
	Serious	NS	Serious	NS	Serious	NS	Serious	NS	Serious	NS
Female	0	0	4	0	3	6	1	8	1	2
Male	0	0	0	1	0	4	3	2	1	3
Unknown	0	0	0	0	0	0	0	0	3	3

Source: RB Health Response to Information Request submitted January 9, 2024, Table 1, page 1.
Abbreviations: FAERS, FDA Adverse Event Reporting System; NS, non-serious

The most common PTs reported among nonserious cases were insomnia (n=4), drug hypersensitivity (n= 4), drug ineffective (n=4), and product use issue (n=3). Table 16 shows the top 10 most frequently reported PTs among nonserious cases.

Table 16. Top Ten Most Frequently Reported Preferred Terms Among Nonserious Cases in FAERS

Preferred Term	Number of Events	Percent of Total Cases Reported
Insomnia	4	8.9%
Drug hypersensitivity	4	8.9%
Drug ineffective	4	8.9%
Product use issue	3	6.7%
Somnolence	2	4.4%
Gait disturbance	2	4.4%
Pain	2	4.4%
Nausea	2	4.4%
Incorrect product administration duration	2	4.4%
Incorrect dose administered	2	4.4%

Source: Adapted from RB Health Response to Information Request submitted January 9, 2024, Table 4, page 8.
Abbreviations: FAERS, FDA Adverse Event Reporting System

The most common PTs reported among serious cases were toxicity to various agents (n=5) and completed suicide (n=3). Table 17 shows the most frequently reported PTs that appear more than once among serious cases.

Table 17. Most Frequently Reported Preferred Terms (>1) Among Serious Cases in FAERS

Preferred Term	Number of Events	Percent of Total Cases Reported
Toxicity to various agents	5	11.1%
Completed suicide	3	6.7%
Bronchopneumonia	2	4.4%
Incontinence	2	4.4%
Abnormal behavior	2	4.4%
Off label use	2	4.4%
Drug ineffective	2	4.4%

Source: Adapted from RB Health Information Request response submitted January 9, 2024, Table 4, page 8.
Abbreviations: FAERS, FDA Adverse Event Reporting System

There were nine fatal outcomes reported. The Applicant provided additional details of the age, [redacted], and PTs reported from these cases. Four fatal cases occurred in those under 18 years of age. All four cases involved females and the PTs associated with these cases were completed

suicide (n=3), toxicity (n=2), overdose/toxicity (n=1), and intentional product misuse (1). Three fatal cases occurred in the 18 to < 65 age group. All three cases involved females and the PTs associated with these cases were abnormal behavior (n=2), bronchopneumonia (n=2), foaming at mouth (n=1), incontinence (n=2), and toxicity to various agents (n=1). A single case occurred in a person greater than 65 years of age. This case involved a male patient and was associated with the PTs of hemorrhagic stroke and internal hemorrhage. One case with an unknown age/ was associated with a PT of drug use disorder.

Notably, all nine fatal cases involved polypharmacy scenarios with between 6 to 15 medications reported in addition to the three main active ingredients. Even though guaifenesin was listed as the primary suspect in one case and naproxen in two cases out of the nine fatal cases reported, due to the limited detailed information available in FAERS database system, it is not possible to conclude that the cause of death was a direct result of the drugs in question.

Overall, the lack of case details in these cases precludes confirmation whether the outcomes (AEs or fatalities) were related to the drugs. However, considering the wide use of nonprescription analgesics/antipyretics, cough, and cold preparations including guaifenesin, dextromethorphan, and naproxen, it is reassuring that the total number of concomitant cases that were reported over 10 years was very small.

7.6.2.1.3. WHO Vigibase

The WHO Vigibase is the adverse drug report database maintained by the Uppsala Monitoring Centre in Sweden. Vigibase collects summaries of clinical reports about individual suspected adverse reactions to pharmaceutical products from national centers in countries participating in the WHO safety program. Case narratives are not available from Vigibase due to international confidentiality restrictions.

The focus of this review is on cases reporting concomitant use of all three active ingredients during the 10-year period from July 1, 2013, to June 30, 2023. The Applicant identified a total of 53 cases in WHO Vigibase. When age was reported, two cases (2/53; 3.8%) involved adolescents ages 12 to less than 18 years, and a majority of 33 cases (33/53; 62.3%) involved adults greater than 18 years. No cases involved individuals less than 12 years. When was reported, the majority of cases were reported in females (29/53; 54.7%) compared with males (14/53; 26.4%).

Of the 53 total cases identified, 14 cases (14/53; 26.4%) were assessed as serious, 38 cases (38/53; 71.7%) were assessed as nonserious, and one case was assessed as having unknown seriousness. The patient characteristics including age, , and seriousness for all cases can be found in Table 18.

Table 18. WHO Vigibase Patient Characteristics of Serious Cases Involving Concomitant Use of Three Active Ingredients

	<12 Years		12 - <18 Years		18- <65 Years			65 + Years		Unknown Age	
	Serious	NS	Serious	NS	Serious	NS	Unknown	Serious	NS	Serious	NS
Female	0	0	1	0	2	7	1	4	10	1	3
Male	0	0	0	0	1	4	0	2	2	1	3
Unknown	0	0	0	0	0	0	0	0	0	2	8

Source: RB Health Response to Information Request submitted January 9, 2024, Table 5, page 14.
Abbreviations: NS, non-serious; WHO, World Health Organization

The most common PTs reported among nonserious cases were drug ineffective (n=7), insomnia, (n=4), drug hypersensitivity (n= 3), and product use issues (n= 3)). Table 19 shows the top ten most frequently reported PTs that appear among nonserious cases.

Table 19. Top Ten Most Frequently Reported Preferred Terms Among Nonserious Cases in WHO Vigibase

Preferred Term	Number of Events	Percent of Total Cases Reported
Drug ineffective	7	13.21%
Insomnia	4	7.5%
Drug hypersensitivity	3	5.7%
Product use issue	3	5.7%
Diarrhea	2	3.8%
Nausea	2	3.8%
Fatigue	2	3.8%
Gait disturbance	2	3.8%
Incorrect dose administration	2	3.8%
Headache	2	3.8%

Source: Adapted from RB Health Response to Information Request submitted January 9, 2024, Table 7, page 16.
Abbreviations: WHO, World Health Organization

The most common PTs reported among serious cases were drug ineffective (n=3) and off label use (n=3). Table 20 shows the most frequently reported PTs that appear more than once among serious cases.

Table 20. Most Frequently Reported Preferred Terms (>1) Among Serious Cases in WHO Vigibase

Preferred Term	Number of Events	Percent of Total Cases Reported
Drug ineffective	3	5.7%
Off label use	3	5.7%
Loss of consciousness	2	3.8%
Neuropathy peripheral	2	3.8%
Hallucinations	2	3.8%

Source: Adapted from RB Health Information Request response submitted January 9, 2024, Table 7, page 16.
Abbreviation: WHO, World Health Organization

Three fatal outcomes reported noted multiple additional medications used in addition to the three active ingredients. Based on the limited available information obtained from this spontaneous adverse reporting system, it is not possible to conclude whether the cause of death was directly caused by contribution of the drugs in question.

Similar to observations noted from the FAERS data, the lack of case details in these cases precludes confirmation whether the outcomes (AEs or fatality) were related to the drugs. However, overall, considering the wide use of nonprescription analgesics/antipyretic, cough, and

cold preparations including guaifenesin, dextromethorphan and naproxen, it is reassuring that the total number of concomitant cases that were reported were very small.

7.6.2.1.4. National Poison Data System

The Applicant conducted a search of the NPDS for cases involving concomitant use of the three single ingredients between January 1, 2023, to July 1, 2023. The information on the three single ingredients did not reveal relevant safety issues for the review of concomitant use of the three active ingredients in this FDC product.

7.6.2.2. Literature Review

The Applicant initially conducted a search of the published literature using PubMed to identify relevant findings for Mucinex DM over the last five years, from 2019-2023. Since the focus of this review is to analyze published literature relevant to the concomitant use of the three active ingredients, the Applicant was requested to conduct a search of literature relevant to the clinical safety of concomitant use of the three drugs in the FDC product covering the last five years. In the three databases (PubMed, PubMed Central, and Google Scholar) that were queried, no literature examining the concomitant use of guaifenesin, dextromethorphan, and naproxen were identified.

7.6.2.3. 120-Day Safety Update

A 120-day safety update was received from the Applicant on March 3, 2024. None of the additional information submitted altered the safety review of the product.

7.7. Key Safety Review Issues

7.7.1. Clinical Safety of the Proposed Product

Background

The Applicant proposes a new drug product that contains a FDC of three active ingredients guaifenesin, dextromethorphan HBr, and naproxen sodium in an ER tablet. Safety data generated from the pivotal PK study were assessed to evaluate the safety of this product (see Section 7.6.1.1 for more details). Additionally, two exploratory PK studies were conducted. Though these studies evaluated earlier formulations of a FDC product, the investigational products contained the same three active ingredients. Therefore, these studies were also assessed for any safety signals (see Section 17 for more details).

Assessment

Safety assessments were conducted for the pivotal PK Study RB5-US-1505 and two pilot Studies 2009-GGE-TRI-DM and 2014-MUCDM-NAP-02.

Safety Results

A total of 157 subjects were randomized across all three PK studies and received at least one dose of the study drug. Overall, a total of 69 subjects (69/157; 43%) reported 144 TEAEs. Of the 144 TEAEs, 143 (143/144; 99.3%) were considered mild in severity, and one (1/144; 0.7%) was considered moderate in severity. TEAEs were all reported as resolved by the end of the study with the exception of three TEAEs with unknown resolution related to one subject who was lost to follow up. Table 21 lists all drug-related TEAEs pooled from the three studies.

Table 21. Pooled Drug-Related TEAEs in Pivotal Study RB5-US-1505 and Pilot Studies 2009-GGE-TRI-DM and 2014-MUCDM-NAP-02

Drug-Related Treatment-Emergent Adverse Event	Number of Reports
Headache	19
Dizziness	18
COVID-19 Infection	16
Diarrhea	5
Nausea	4
Vomiting	4
Abdominal pain	3
Feeling Relaxation	3
Hemoglobin decrease	3
Fatigue	3
Back Pain	3

Source: Reviewer generated.
Abbreviations: COVID-19, coronavirus disease 2019; TEAE, treatment-emergent adverse event

There were no deaths or serious adverse events reported. A total of 44 subjects discontinued from the studies, but the majority of the discontinuations were not due to AEs from the study drug. A large percentage of discontinuations was due to COVID-19 infection.

Conclusion

Clinical safety data showed that most AEs were mild and self-limited. Almost all AEs had resolved by the end of the study. When potentially related to study drug, the AEs reported were consistent with AE profiles of the single ingredients across all three studies. Overall, the clinical safety data suggests that the safety profile of the FDC product is similar to that of the listed drugs.

7.7.2. Safety Data From Postmarketing Safety and Literature Review Support Safe Use of the Proposed Product

Background

The proposed FDC of these three ingredients is not approved in the U.S. market or in any foreign market. However, single ingredient products (containing guaifenesin, dextromethorphan HBr, or naproxen sodium alone) and combinations containing guaifenesin and dextromethorphan HBr have been marketed for decades in the nonprescription setting. The Applicant identified and evaluated cases reporting involvement of all three active ingredients in the postmarket setting over

a 10-year period to understand the potential safety issues that may arise with concomitant use of the three active ingredients.

Assessment

The Applicant assessed postmarketing safety data using the company's own internal pharmacovigilance database, FAERS, WHO Vigibase, the NPDS, and the published literature. Overall, the total number of cases reporting concomitant use of the three active ingredients was low. There were few serious cases and even fewer fatal cases. Fatal cases uniformly reported significant polypharmacy, thereby precluding a conclusion of causality. The top PTs reported included insomnia, drug hypersensitivity, drug ineffectiveness, and product use issue. The databases were overall consistent with each other.

Conclusion

FDA's review of the Applicant's search and assessment of the postmarketing safety data revealed no new safety signals or concerns associated with concomitant use of guaifenesin, dextromethorphan, and naproxen.

7.7.3. Proposed Product Does Not Present an Increased Risk for Dextromethorphan Abuse

Background

The proposed product is an ER combination product containing dextromethorphan HBr. Dextromethorphan has been marketed for over 50 years and is presently available in several nonprescription drug products. It is a known drug of abuse (Nordt 1998). Consistent with its main mechanism of action at NMDA receptors, dextromethorphan at high doses can produce hallucinogenic and dissociative effects as well as cognitive impairment (Carter et al. 2013). Nonetheless, dextromethorphan is not scheduled under the Controlled Substances Act.

In the proposed product, the Applicant has developed a bilayer tablet consisting of an MR layer, (b) (4), and an IR layer, (b) (4). There is 30 mg of dextromethorphan HBr in each tablet.

Reviewers from CSS were consulted to evaluate the abuse and misuse potential of dextromethorphan in the proposed product.

Assessment

In the CSS consult, Dr. Chad Reissig noted that the proposed drug does not contain a dose of dextromethorphan HBr that is greater than that of currently marketed dextromethorphan-containing products. Additionally, Dr. Reissig reviewed the results of the clinical PK Study RB5-US-1505 for AEs associated with abuse potential. These are indicated in Table 22.

Table 22. Abuse-Related Adverse Events in Study RB5-US-1505

Preferred Term	All subjects (N=102) n (%)	Treatment A (N=83 n (%)	Treatment B (N=82) n (%)	Treatment C (N=79) n (%)	Treatment D (N=76) n (%)
Feeling abnormal	2* (1.96)	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

Source: Adapted from eCTD Module 5.3.1. Clinical Study Report Table 12-64 Treatment-Emergent Adverse Events-MedDRA.
*Dr. Reissig's consult noted three subjects reporting the PT Feeling abnormal; however, two subjects were noted to have reported feeling abnormal per the Applicant's data table referenced above.
Abbreviations: N, number (of population); n, number (of sample)

Overall, it was noted that few abuse-related AEs occurred. A total of four AEs were reported in three subjects. There were no AEs of "euphoric mood," or "hallucination" expected with an NMDA antagonist.

Separately, Dr. Reissig also noted that prior clinical studies of the recreational effects of dextromethorphan utilized much higher doses of dextromethorphan than those examined in the clinical PK study and proposed for use in the current product.

Conclusion

The proposed FDC product does not contain an amount of dextromethorphan HBr that is greater than that currently marketed for dextromethorphan-containing products. In a clinical study, the product did not demonstrate significant AEs that would signal an abuse potential. Therefore, Dr. Reissig concludes that the proposed product does not present an increased abuse potential relative to existing FDA-approved products containing dextromethorphan. No specific actions and no additional labeling information beyond class labeling was considered necessary for the proposed product relative to the concern of misuse and abuse potential of dextromethorphan.

For further details, refer to the Dr. Reissig's consult memorandum dated January 22, 2024 (DARRTS Reference ID:5314327).

8. Therapeutic Individualization

8.1. Intrinsic Factors

The Applicant did not provide any new information on the influence of intrinsic factors such as age, , race, or ethnic differences on the AE profile of the proposed FDC product. Nonetheless, as each of the ingredients of this proposed product has demonstrated BE with approved listed drugs, Mucinex DM and Aleve, the proposed drug is expected to carry potential risks similar to those of its three active ingredients.

Certain populations such as the elderly and pregnant/breastfeeding women are expected to be more vulnerable to AEs. Consumers with certain diseases such as GI, CV conditions, renal disease, asthma, chronic cough (such as occurs with smoking, chronic bronchitis, or emphysema), allergic conditions, and liver disease are also considered to be at higher risk.

Class labeling for nonprescription NSAIDs, dextromethorphan, and guaifenesin address these intrinsic factors by excluding those with comorbidities from nonprescription use and limiting the

dose and duration of use. No additional warnings relating to other intrinsic factors were determined to be necessary.

8.2. Extrinsic Factors

There is no known drug-drug interaction among the three active ingredients in this FDC product. The PK program in current NDA 217338 did not assess the drug interaction potential for the three active ingredients. However, the drug-drug interaction potential between dextromethorphan and guaifenesin was assessed during clinical development of Mucinex DM (NDA 021062). In Study 2002-15 under NDA 021062, co-administration of guaifenesin and dextromethorphan did not impact each other's exposure indicting no interaction between these two drugs. Based on available in vitro data and clinical use experience, guaifenesin, dextromethorphan and naproxen are not known to modulate drug metabolic enzymes, such as the cytochrome P450 (CYP) system or Phase 2 metabolism.

Pivotal Study RB5-US-1505 did not demonstrate an apparent food effect for guaifenesin and naproxen, while it showed increased exposure for dextromethorphan to a similar extent to the listed drug, which supports that the drug product can be taken regardless of food.

The Applicant conducted an in vitro dose dumping study to evaluate the effect of alcohol intake with the proposed FDC product and concluded that alcohol does not significantly impact dissolution of the three ingredients differently than with the listed drugs. In vivo studies were not required.

Approved labeling for nonprescription Mucinex DM warns consumers not to use the drug if currently taking a prescription monoamine oxidase inhibitor (certain drugs for depression, psychiatric or emotional conditions, or Parkinson's disease) or for two weeks after stopping the monoamine oxidase inhibitor drug. Additionally, the nonprescription labeling for Aleve advises consumers to ask a doctor or pharmacist before use of naproxen products if they are taking any other drug containing an NSAID (prescription or nonprescription), taking a blood thinning (anticoagulant) or steroid drug, under a doctor's care for any serious condition or taking any other drug.

The Applicant proposes to retain all warnings from both Mucinex DM and Aleve for the proposed FDC drug product. No additional warnings relating to other extrinsic factors were determined to be necessary.

8.3. Plans for Pediatric Drug Development

Because the FDC product represents a new active ingredient and a new dosage form, the Applicant was required to submit an initial pediatric study plan in accordance with the Pediatric Research Equity Act. The initial pediatric study plan proposed a request for pediatric waiver in children less than 12 years and extrapolation to support use in children older than 12. This was discussed by the Pediatric Research Committee on January 23, 2019, and the Applicant received an agreed PSP on June 1, 2019.

In this application and consistent with the agreed PSP, the Applicant has requested a partial waiver of pediatric studies in children under 4 years because the drug would be unsafe. The

Applicant highlighted that a waiver in this age group would be consistent with recommendations from medical societies such as the American Academy of Pediatrics (AAP 1997; AAP 2021; Laurie Seidel Halmo et al. 2022) and actions taken by manufacturers to change the labeling for nonprescription cough and cold medicines to include a statement, "do not use in children under four years of age."

The Applicant has also requested a partial waiver for children 4 to less than 12 years of age because ER products are not appropriate for nonprescription use in younger children due to the need of having the child evaluated by a learned intermediary. This is particularly so when IR formulations of guaifenesin, dextromethorphan, and NSAIDs are already available in the nonprescription setting for children in this age group. The proposed product would not represent a meaningful therapeutic benefit over existing therapies and would not likely be used in a substantial number of pediatric patients.

The Applicant proposed to use the same dosing instructions for children 12 to less than 18 years of age as that for adults. This would mirror the dosing directions of the listed products, Mucinex DM and Aleve, which are both approved for use in children older than 12 years with the same directions as for adults. The pediatric assessment is based on the premise that the course of the disease and the effects of the active ingredients are sufficiently similar in adults and pediatric patients 12 years and older. Since the adult PK study demonstrated BE of each of the components of the FDC product with its corresponding listed drug, Mucinex DM or Aleve, the adult PK data could be used to extrapolate safety and efficacy to the pediatric population down to 12 years without the need of pediatric studies. Additionally, the Applicant conducted PBPK modeling analysis to further support the extrapolation of the adult PK data to adolescents 12 to 17 years. The review of the PBPK modeling can be found in Section 14.5. While the PBPK modeling analysis was considered inadequate for the intended purpose, it is noted that this additional assessment was not required to support pediatric use of this product.

No new nonclinical studies or pediatric clinical studies were conducted to support pediatric use of this new FDC product. The proposed product contains no novel excipients, and no reformulation was needed for the proposed pediatric use.

Proposed labeling for this product states "Do not use" for children under 12 years of age.

8.4. Pregnancy, Lactation, and Females/Males of Reproductive Potential

The Applicant did not conduct studies that provide data on human reproduction and pregnancy.

The proposed labeling for this product will address pregnancy and breast-feeding concerns by containing the same pregnancy and breast-feeding warnings that are on both the Mucinex DM and Aleve labels. Pregnant and breast-feeding consumers are advised to ask a health professional before use. The label will further advise consumers "not to use naproxen sodium at 20 weeks or later in pregnancy unless definitely directed to do so by a doctor because it may cause problems in the unborn child or complications during delivery."

No additional labeling is recommended on this issue.

9. Product Quality

Approval

The OPQ review team has assessed NDA 217338 with respect to chemistry, manufacturing, and controls and has determined that it meets all applicable standards to support the identity, strength, quality, and purity that it purports. As such OPQ recommends approval of this NDA from a quality perspective.

Regarding quality aspects of the application, the drug substance, drug product, biopharmaceutics, process, and facility sections were reviewed during the review cycle and found adequate to support the approval of the application.

The drug substance and drug product manufacturing facilities appear capable of the proposed operations based on the firm's experience with the dosage form manufacturing and current good manufacturing practice compliance status. The manufacturing process involves (b) (4) (b) (4)

The drug product has been granted a shelf life of 36 months when stored at 20-25°C (68-77°F) in all proposed container closure configurations.

In brief, the chemistry, manufacturing, and controls review has identified no outstanding issue and the provided information is adequate to support approval of the NDA from OPQ's perspective.

9.1. Device or Combination Product Considerations

Not applicable.

10. Human Subjects Protections/Clinical Site and Other Good Clinical Practice Inspections/Financial Disclosure Review

A request was submitted to the Office of Study Integrity and Surveillance (OSIS) for inspection as part of Prescription Drug User Fee Act preapproval clinical investigation and data validation of the pivotal BA studies. In the consult memo, OSIS staff declined to conduct a new inspection because the Office of Regulatory Affairs had conducted an inspection in November 2022 and a Remote Regulatory Assessment inspection of the analytical site had been conducted in (b) (4) (b) (4). Because OSIS concluded that data from the previous inspections were considered reliable, no new inspection was warranted for this application (OSIS memorandum, November 7, 2023; DARRTS Reference ID: 5274033).

There was one covered clinical study in this NDA involving a total of 14 clinical investigators. An FDA form 3454 was submitted for the study and covered all the clinical investigators. There were no disclosed financial interests or arrangements identified.

11. Advisory Committee Summary

As no review issues were determined to require discussion by outside experts, an advisory committee meeting was not held during this marketing application review.

III. Additional Analyses and Information

12. Summary of Regulatory History

Table 23. Key Presubmission Meetings and Milestones

Date/Activity	Outcome
June 5, 2009: IND Opening Protocol submission	RB Health opened IND 105403 with a proof-of-concept Phase 1 PK study. The Applicant had prepared two formulations of a modified- release bilayer tablet. A "(b) (4) version of the product was to be used in the pilot PK study to determine the optimal final formulation. The two experimental formulations differed in the (b) (4) (b) (4) The study was deemed safe to proceed.
December 16, 2009: Advice Letter/Information Request	FDA informed the Applicant that its proposed 505(b)(2) approach appeared appropriate. FDA advised the Applicant to define the population who will benefit from this combination product. FDA also advised the Applicant to address the PREA. FDA raised concerns regarding dose dumping. FDA recommended that the Applicant evaluate drug-alcohol interaction with the ER product. FDA recommended to include subjects with CYP2D6 poor metabolizer phenotype in the proposed pilot BA Study 2009-GGE-TRI-DM.
April 12, 2011: Type C meeting	A meeting was held to discuss the target population, PK program, and PREA requirements. FDA agreed that the proposed combination may be rational for a target population with upper respiratory infection symptoms including cough, fever, and pain.
July 27, 2015: Type C meeting	A meeting was held to discuss the development plan of (b) (4) which RB Health proposed (b) (4) (b) (4) . FDA noted that the PK approach relying on Mucinex DM and Aleve appeared reasonable, but requested the Applicant to demonstrate that the PK profiles support a 12-hour dosing regimen. Regarding the Applicant's proposed indication " (b) (4) (b) (4) " FDA (b) (4) (b) (4) (b) (4)

Date/Activity	Outcome
	(b) (4) [redacted]
March 7, 2016: Type C WRO	This meeting was held to discuss the Applicant's proposed (b) (4) dosage form to develop a new ER bilayer tablet consisting of an immediate-release layer and a modified release layer. FDA agreed the proposed PK program may support a 505(b)(2) NDA; however, reiterated that the Applicant needed to "demonstrate that the PK profile of [its] product supports a 12-hour dosing regimen." FDA agreed a multiple dose study, or a drug-drug interaction study is not required. FDA advised the need to develop new dissolution methods and the need to conduct an in vitro alcohol dose dumping study.
November 8, 2016: Proprietary name review	The proposed proprietary name, (b) (4), was deemed conditionally acceptable.
June 1, 2019: Agreed iPSP	FDA issued an agreed iPSP. The Applicant requested partial waivers of pediatric assessments for 1) children birth to less than 4 years and 2) children 4 to below 12 years of age. The Applicant proposed a pediatric assessment for children 12 to less than 18 years based on extrapolation of PK, efficacy and safety data from the adult clinical program that is based on the premise that the course of the disease and the effects of the drug are sufficiently similar in adult and pediatric patients.
June 5, 2023: Type B pre-NDA meeting	This meeting was held to discuss format and content for the expected NDA, including proposed indications, age restrictions, and dosing recommendations. Extensive advice was provided from CMC, clinical pharmacology, clinical, and labeling perspectives. The Applicant provided topline PK results. FDA highlighted a potential issue that the dosing interval (every 12 hours) represents a modification of the dosing interval for listed drug Aleve, which is taken every 8-12 hours. FDA inquired what consumers were supposed to do if pain/fever returned prior to 12 hours of dosing. FDA advised the Applicant to provide data/information to support proposed fixed 12-hour dosing interval. FDA reiterated that the indication and claims related to (b) (4) were not supported by the listed products.

Source: Reviewer generated
Abbreviations: BA, bioavailability; CMC, chemistry, manufacturing, and controls; DM, dextromethorphan; ER, extended-release; FDA, Food and Drug Administration; HBr, hydrobromide; Hr., hour; IND, investigational new drug application; IR, immediate-release; iPSP, initial pediatric study plan; NDA, new drug application; PK, pharmacokinetic; PREA, Pediatric Research Equity Act; WRO, written response only

13. Pharmacology Toxicology

13.1. Summary Review of Studies Submitted With the Investigational New Drug Application

Not applicable.

13.2. Individual Reviews of Studies Submitted With the New Drug Application

Not applicable.

14. Clinical Pharmacology

14.1. In Vitro Studies

No clinical pharmacology in vitro studies were submitted under this new drug application (NDA).

14.2. In Vivo Studies

14.2.1. Summary of Clinical PK Findings in Pivotal Study RB5-US-1505

Study Design and Treatments

Study RB5-US-1505 was an open-label, randomized, balanced, single-dose, four-treatment, four-period, crossover relative bioavailability (BA) study. The primary objective was to assess the relative BA of each of the three active ingredients (guaifenesin, dextromethorphan, and naproxen) from the proposed drug product and the listed products, a combination of Mucinex DM (NDA 021620) and Aleve (NDA 020204), in healthy adults in the fasted state.

In addition, this study assessed the food effect on pharmacokinetics (PK) of each of the three active ingredients following administration of the proposed product and listed drug products.

In this study, a total of 102 healthy subjects were enrolled and dosed in this study. Subjects were randomized to receive following treatments in a cross-over manner:

- Treatment A: Two Mucinex 12 HR Cold & Fever Multi-Symptom tablets after 10-hour fast
- Treatment B: Two Mucinex 12 HR Cold & Fever Multi-Symptom after a high-fat meal
- Treatment C: Two Mucinex DM tablets and one Aleve tablet after 10-hour fast
- Treatment D: Two Mucinex DM tablets and one Aleve tablet after a high-fat meal

There was a 10-day washout period after the administration of each treatment. Total doses in each of the four treatment arms were 1200 mg for guaifenesin, 60 mg for dextromethorphan hydrobromide (HBr), and 220 mg for naproxen sodium. There were no major protocol deviations impacting the study outcome. Only one major deviation noted was an early termination (Subject (b) (6) due to an indeterminate pregnancy test.

PK Sampling

Blood samples were drawn pre-dose and at 0.125, 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 7, 8, 9, 10, 11, 12, 14, 16, 18, 21, 24, 36, 48, 72, and 96 hours post-dose. Fluids were withheld from 1 hour before dosing until 1 hour after dosing. At each sampling time point 4 mL of blood was taken from each subject into a K2EDTA tube; thus, approximately 480 mL of blood was collected from each subject who participated in all four treatment arms.

Data Analysis

Noncompartmental analysis was carried out with Phoenix WinNonlin to determine maximum plasma concentration (C_{max}), area under the concentration-time curve up to the last measurable concentration (AUC_{0-t}), area under the concentration-time curve estimated to infinity (AUC_{inf}), $t_{1/2}$, and time to maximum concentration (T_{max}) for all three active ingredients. For naproxen, partial area under the concentration-time curve (AUC) assessment was conducted to AUC_{0-12h}. The 90% confidence interval (CI) of the geometric least square mean ratio (test/reference) of the main endpoints was calculated using Phoenix WinNonlin bioequivalence (BE) scheme considering the following pairs for all three active ingredients:

- Primary BE assessment: Treatment A (Test) versus Treatment C (Reference).
- Food effect on PK of three active ingredients following administration of proposed drug product: Treatment B versus Treatment A.
- For this food effect assessment, the reference arm was the proposed drug product under fasted condition (Treatment A) and the test arm was the proposed drug product under fed condition (Treatment B).
- Food effect on PK of dextromethorphan following administration of listed drug: Treatment D versus Treatment C.
- For this food affect assessment, the reference arm was the listed drugs under fasted condition (Treatment C) and the test arm was the listed drugs under fed condition (Treatment D).

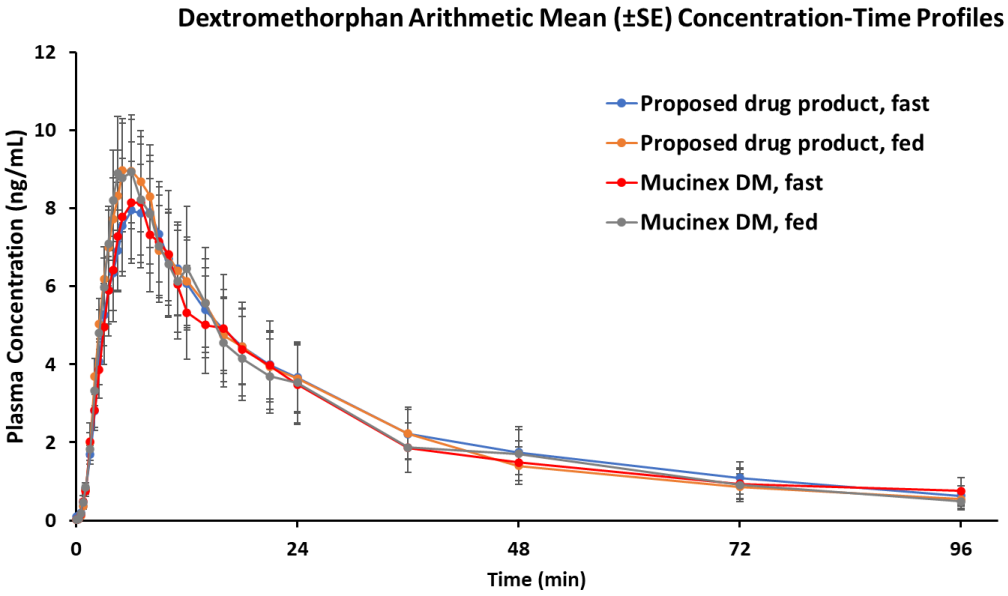
PK Results

A total of 102 healthy subjects (male, n= 53; female, n=49) were enrolled and included in the full analysis set and PK population, of which 61 subjects completed all four treatment periods. The mean and standard deviation for age and body weight for the subjects were 32.8 (±10.02) years and 76.59 (±13.226) kg, respectively. Overall, 22 subjects (22/102; 21.57%) were discontinued due to treatment-emergent adverse events (TEAEs), 16 of which were discontinued due to coronavirus disease 2019 infection. PK parameters from all subjects who had evaluable concentration were determined using noncompartmental analysis except two subjects in two treatment arms (Subject (b) (6) in treatment arm D, and Subject (b) (6) in treatment arm B) because of inadequate PK samples.

PK Results for Dextromethorphan

Dextromethorphan arithmetic mean PK profiles by treatment arm are displayed in Figure 1. Dextromethorphan arithmetic mean PK parameters are summarized in Table 24. The result of statistical comparison of dextromethorphan systemic exposures between the proposed product and the listed drug is summarized under fasted condition in Table 25. BE is established for dextromethorphan under fasted condition.

Figure 1. Observed Arithmetic Mean PK Profiles of Dextromethorphan Following 60 mg Single Dose in Study RB5-US-1505



Source: FDA analysis using ADPC.xpt from Study RB5-US-1505
Abbreviations: DM, dextromethorphan; mg, milligram; mL, milliliter; ng, nanogram; PK, pharmacokinetic; SE, standard error

Table 24. Summary of Mean ± SD PK Parameters of Dextromethorphan in Study RB5-US-1505

Treatment Arm	A (Proposed Drug Product-Fasted Arm) (N=83)	B (Proposed Drug Product-Fed Arm)[1] (N=80)	C (Mucinex DM-Fasted Arm) (N=79)	D (Mucinex DM-Fed Arm) (N=76)
AUC_{inf} [1] (ng·h/mL)	272.12±656.97	301.77±694.62	275.98±750.32	253.27±623.48
AUC_{0-96h} [1] (ng·h/mL)	235.46±511.25	228.48±469.75	230.38±568.25	230.60±537.94
C_{max} (ng/mL)	9.06±12.50	10.65±13.58	9.60±16.68	10.81±15.46
Elimination half-life[1] $t_{1/2}$ (h)	13.19±7.90	13.03±8.22	13.23±8.45	12.34±6.13
T_{max} (h)[2]	6 (1-9)	5 (2-18)	5 (1.5-10)	4.5 (1.5-14)

Source: FDA Analysis using ADPC.xpt from Study RB5-US-1505
[1] AUCs and $t_{1/2}$ values are not available from one subject.
[2] Median (min, max)
Abbreviations: AUC_{inf}, area under the concentration-time curve estimated to infinity; AUC_{0-96h}, area under the concentration-time curve from time 0 to 96 hours; C_{max}, maximum plasma concentration; h, hour; mL, milliliter; N, number (of population); ng, nanogram; SD, standard deviation; T_{max}, time to maximum concentration; $T_{1/2}$, half-life

Table 25. Statistical Comparisons of PK Parameters of Dextromethorphan Under Fasted Conditions, Full Analysis Population

PK Parameters	Listed Drug* Geometric LSM	Proposed Drug Product** Geometric LSM	Proposed/Listed Geometric Ratio [Percentage (90% CI)] (N=68)
C_{max} (ng/mL)	3.41	3.24	95.31 (86.12-105.48)
AUC_{0-96h} (ng.h/mL)	45.37	46.59	102.68 (93.30-113.02)
AUC_{inf} (ng.h/mL)	46.33	47.51	102.54 (93.06-112.99)

Source: FDA Analysis using ADPC.xpt from Study RB5-US-1505
*Proposed drug product under fasted condition (Treatment A: two Mucinex 12 HR Cold & Fever Multi-Symptom tablets after a 10-hour fast)
**Listed drug under fasted condition (Treatment C: two Mucinex DM tablets and one Aleve tablet after a 10-hour fast)
Abbreviations: AUC_{inf}, area under the concentration-time curve estimated to infinity; AUC_{0-96h}, area under the concentration-time curve from time 0 to 96 hours; CI, confidence interval; C_{max}, maximum plasma concentration; h, hour; LSM, least squares mean; mL, milliliter; N, number (of population); ng, nanogram; PK, pharmacokinetic

A high-fat meal increased dextromethorphan C_{max} and AUC_{inf} by 34% and 24%, respectively when following the administration of the proposed drug product (Table 26). Note that similar food effect was observed for the listed drug (i.e., Mucinex DM). A high-fat meal increased dextromethorphan C_{max} and AUC_{inf} by 43% and 22%, respectively when following the administration of the listed drug (Table 26).

Table 26. Statistical Analysis of Food Effect on PK of Dextromethorphan in Study RB5-US-1505

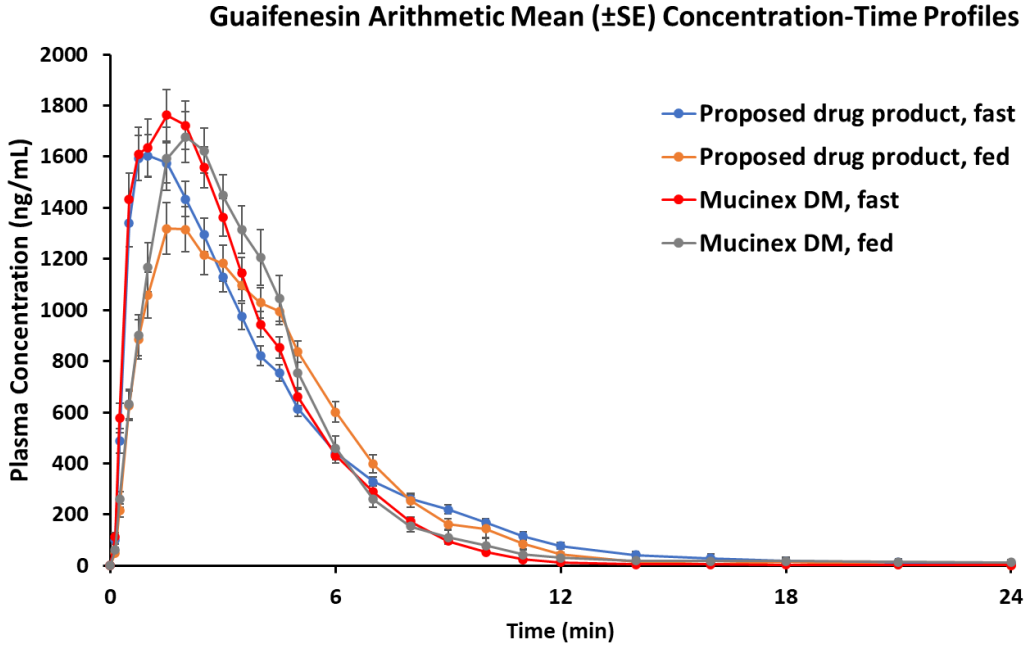
PK Parameters	Treatment A (Proposed Drug Product in Fasted Condition) Geometric LSM	Treatment B (Proposed Drug Product in Fed Condition) Geometric LSM	Treatment B/Treatment A Ratio [Percentage (90% CI)][a] (N=69)
Proposed drug product			
C_{max} (ng/mL)	3.54	4.76	134.145 (120.24-149.65)
AUC_{0-96h} (ng.h/mL)	52.20	64.86	124.24 (112.79-136.85)
AUC_{inf} (ng.h/mL)	53.26	65.85	123.64 (112.14-136.34)
PK Parameters	**Treatment C (Listed Drugs - Fasted Arm) Geometric LSM**	**Treatment D (Listed Drugs – Fed Arm) Geometric LSM**	**Treatment D/Treatment C Ratio [Percentage (90% CI)][b] (N=66)**
Listed drug			
C_{max} (ng/mL)	3.16	4.52	142.59 (126.21-161.09)
AUC_{0-96h} (ng.h/mL)	42.11	51.40	122.04 (109.11-136.51)
AUC_{inf} (ng.h/mL)	42.87	52.21	121.76 (108.83-136.24)

Source: FDA Analysis using ADPC.xpt from Study RB5-US-1505
[a] For this food effect assessment, the reference arm was the proposed drug product in fasted condition (Treatment A: two Mucinex 12 HR Cold & Fever Multi-Symptom tablets after 10-hour fast) and the test arm was the proposed drug product in fed condition (Treatment B: two Mucinex 12 HR Cold & Fever Multi-Symptom tablets followed by high fat standardized meal prior to which subjects fasted for 10 hours overnight)
[b] For this food affect assessment, the reference arm was the listed drugs under fasted condition (Treatment C: two Mucinex DM tablets and one Aleve tablet after 10-hour fast) and the test arm was the listed drugs in fed condition (Treatment D: two Mucinex DM tablets and one Aleve tablet followed by a high fat standardized meal prior to which subjects fasted for 10 hours overnight).
Abbreviations: AUC_{inf}, area under the concentration-time curve estimated to infinity; AUC_{0-96h}, area under the concentration-time curve from time 0 to 96 hours; CI, confidence interval; C_{max}, maximum plasma concentration; h, hour; LSM, least squares mean; mL, milliliter; N, number (of population); ng, nanogram; PK, pharmacokinetic

PK results for guaifenesin

Guaifenesin arithmetic mean PK profiles by treatment arm are displayed in Figure 2. Guaifenesin arithmetic mean PK parameters are summarized in Table 27. The result of statistical comparison of guaifenesin systemic exposures between the proposed product and the listed drug under fasted condition is summarized in Table 31. BE is established for guaifenesin under fasted condition.

Figure 2. Observed Arithmetic Mean PK Profiles of Guaifenesin Following 1200 mg Single Dose in Study RB5-US-1505



Source: FDA analysis using ADPC.xpt from Study RB5-US-1505
Abbreviations: DM, dextromethorphan; mg, milligram; min, minute; mL, milliliter; ng, nanogram; PK, pharmacokinetic; SE, standard error

Table 27. Summary of Mean ± SD PK Parameters of Guaifenesin in Study RB5-US-1505

Treatment Arm	A (Proposed Drug Product-Fasted Arm) (N=83)	B (Proposed Drug Product – Fed Arm) (N=81)	C (Mucinex DM – Fasted Arm) (N=79)	D (Mucinex DM-Fed Arm) (N=76)
AUC_{inf} (ng·h/mL)	8058.90±3240.55	7532.11±2864.55	8001.80±2949.30	8171.63±4495.06
AUC_{0-24h} (ng·h/mL)	8026.11±3242.85	7489.15±2866.35	7966.80±2950.73	8128.63±4498.91
C_{max} (ng/mL)	1870.54±792.68	1671.38±936.96	2145.99±1053.45	2174.36±1093.44
Elimination half-life, $t_{1/2}$ (h)	8.96±2.06	11.07±3.19	9.70±1.47	11.92±2.49
T_{max} (h)[1]	1 (0.5-11)	2.5 (0.5-10)	1.5 (0.5-7)	2.5 (1-18)

Source: FDA Analysis using ADPC.xpt from Study RB5-US-1505
[1] Median (min- max)
Abbreviations: AUC_{inf}, area under the concentration-time curve estimated to infinity; AUC_{0-24h}, area under the concentration-time curve from time 0 to 24 hours; C_{max}, maximum plasma concentration; h, hour; mL, milliliter; N, number (of population); ng, nanogram; PK, pharmacokinetic; SD, standard deviation; T_{max}, time to maximum concentration; $T_{1/2}$, half-life

Table 28. Statistical Comparisons of PK Parameters of Guaifenesin Under Fasted Conditions, Full Analysis Population

PK Parameters	Listed Drug* Geometric LSM	Proposed Drug Product** Geometric LSM	Proposed/Listed Geometric Ratio [Percentage (90% CI)] (N=68)
C_{max} (ng/mL)	1966.82	1774.75	90.23 (85.46-95.26)
AUC_{0-24h} (ng.h/mL)	7384.41	7320.21	99.13 (95.35-103.05)
AUC_{inf} (ng.h/mL)	7605.26	7579.21	99.65 (95.63-103.85)

Source: FDA Analysis using ADPC.xpt from Study RB5-US-1505
* Proposed drug product under fasted condition (Treatment A: two Mucinex 12 HR Cold & Fever Multi-Symptom tablets after 10-hour fast)
** Listed drug under fasted condition (Treatment C: two Mucinex DM tablets and one Aleve tablet after 10-hour fast)
Abbreviations: AUC_{inf}, area under the concentration-time curve estimated to infinity; AUC_{0-24h}, area under the concentration-time curve from time 0 to 24 hours; CI, confidence interval; C_{max}, maximum plasma concentration; h, hour; LSM, least squares mean; mL, milliliter; N, number (of population); ng, nanogram; PK, pharmacokinetic

A high-fat meal does not have an effect on C_{max} and AUC_{inf} of guaifenesin, as the 90% CI of the geometric mean ratios were within the range of 0.8 and 1.25 (Table 29). A high-fat meal delays the median T_{max} of guaifenesin by 1.5 hours in the proposed drug product arm. However, the clinical significance of this delay is unclear.

Table 29. Statistical Analysis of Food Effect on PK of Guaifenesin in Study RB5-US-1505

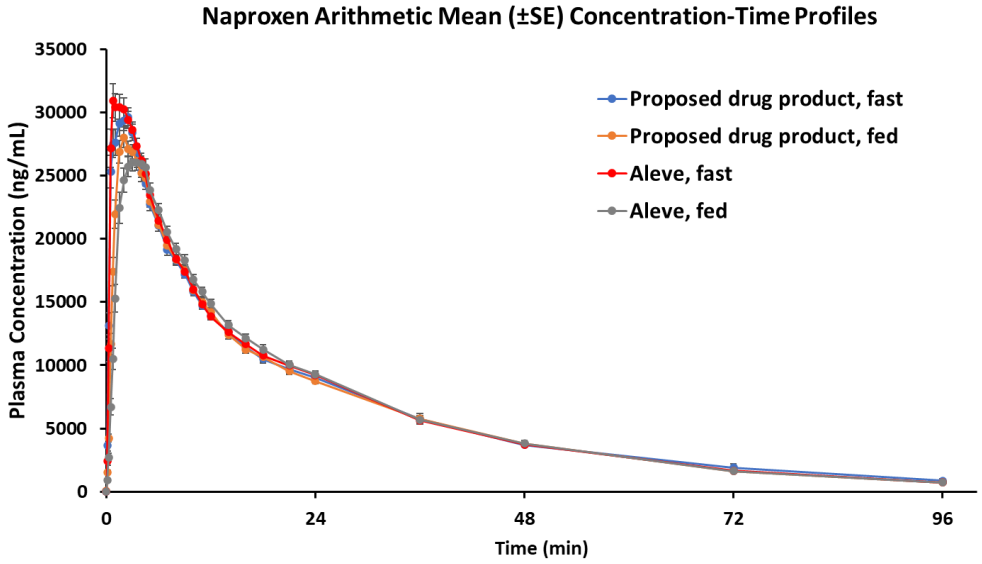
PK Parameters	Treatment A (Proposed Drug Product in Fasted Condition)[a] Geometric LSM	Treatment B (Proposed Drug Product in Fed Condition)[b] Geometric LSM	Fed/Fasted Ratio [Percentage (90% CI)] (N=70)
C_{max} (ng/mL)	1732.0212	1512.32	87.31 (81.25-93.83)
$AUC_{(0-24h)}$ (ng.h/mL)	7226.2572	6931.66	95.92 (92.36-99.61)
AUC_{inf} (ng.h/mL)	7481.5392	7161.63	95.72 (91.83-99.78)

Source: FDA Analysis using ADPC.xpt from Study RB5-US-1505
[a] The reference arm is the proposed drug product under fasted condition (Treatment A: two Mucinex 12 HR Cold & Fever tablets after 10-hour fast)
[b] The test arm is the proposed drug product under fed condition (Treatment B: two Mucinex 12 HR Cold & Fever Multi-Symptom tablets followed by a high fat standardized meal prior to which subjects fasted for 10 hours overnight)
Abbreviations: AUC_{inf}, area under the concentration-time curve estimated to infinity; AUC_{0-24h}, area under the concentration-time curve from time 0 to 24 hours; CI, confidence interval; C_{max}, maximum plasma concentration; h, hour; LSM, least squares mean; mL, milliliter; N, number (of population); ng, nanogram; PK, pharmacokinetic

PK results for naproxen

Naproxen arithmetic mean PK profiles by treatment arm are displayed in Figure 3. Naproxen arithmetic mean PK parameters are summarized in Table 29. The result of statistical comparison of naproxen systemic exposures between the proposed product and the listed drug under fasted condition is summarized in Table 31. BE is established for dextromethorphan under fasted condition.

Figure 3. Observed Arithmetic Mean PK Profiles of Naproxen Following 220 mg Single Dose in Study RB5-US-1505



Source: FDA Analysis using ADPC.xpt from Study RB5-US-1505
Abbreviations: mg, milligram; min, minute; mL, milliliter; ng, nanogram; PK, pharmacokinetic; SE, standard error

Table 30. Summary of Mean ± SD PK Parameters of Naproxen in Study RB5-US-1505

Treatment arm	A (Proposed Drug Product – Fasted Arm) (N=83)	B (Proposed Drug Product – Fed Arm) (N=81)	C (Listed drugs – Fasted Arm) (N=79)	D (Listed drugs – Fed Arm) (N=76)
AUC_{inf} (ng.h/mL)	662784.36 ±218514.68	624415.18 ±154348.34	652111.70 ±136980.90	637862.51 ±136345.08
$AUC_{0\text{-}96h}$ (ng.h/mL)	622895.71 ±152604.37	598130.92 ±150952.01	627560.21 ±129751.97	612217.64 ±129153.92
C_{max} (ng/mL)	36302.41 ±7866.14	32623.46 ±6432.58	38202.53 ±8352.67	31192.11 ±6637.32
Elimination half-life $t_{1/2}$ (h)	20.43 ±5.39	19.30 ±3.85	19.83 ±3.54	19.51 ±3.65
T_{max} (h)	1.5 (0.5-18)	2 (0.75-36)	1 (0.5-7)	3 (0.75-18)

Source: FDA Analysis using ADPC.xpt from Study RB5-US-1505
Abbreviations: AUC_{inf}, area under the concentration-time curve estimated to infinity; $AUC_{0\text{-}96h}$, area under the concentration-time curve from time 0 to 96 hours; C_{max}, maximum plasma concentration; h, hour; mL, milliliter; N, number (of population); ng, nanogram; PK, pharmacokinetic; SD, standard deviation; $t_{1/2}$, half-life

Table 31. Statistical Comparisons of PK Parameters of Guaifenesin Under Fasted Conditions, Full Analysis Population

PK Parameters	Listed Drug* Geometric LSM	Proposed Drug Product** Geometric LSM	Proposed/Listed Geometric Ratio [Percentage (90% CI)] (N=68)
C_{max} (ng/mL)	37976.34	36541.93	96.22 (92.43-100.17)
AUC_{0-96h} (ng.h/mL)	631689.28	634631.18	100.46 (97.50-103.52)
AUC_{inf} (ng.h/mL)	656452.96	667355.92	101.66 (97.80- 105.66)
AUC_{0-12h} (ng.h/mL)	258700.74	254102.21	98.22 (96.46-100.01)

Source: FDA analysis using ADPC.xpt from Study RB5-US-1505
* Proposed drug product under fasted condition (Treatment A: two Mucinex 12 HR Cold & Fever Multi-Symptom tablets after 10-hour fast)
** Listed drug under fasted condition (Treatment C: two Mucinex DM tablets and one Aleve tablet after 10-hour fast)
Abbreviations: AUC_{inf}, area under the concentration-time curve estimated to infinity; AUC_{0-12h}, area under the concentration-time curve from time 0 to 12 hours; AUC_{0-96h}, area under the concentration-time curve from time 0 to 96 hours; CI, confidence interval; C_{max}, maximum plasma concentration; LSM, least squares mean; mL, milliliter; N, number (of population); ng, nanogram; PK, pharmacokinetic

A high-fat meal does not have an effect on C_{max} and AUC_{inf} of naproxen, as the 90% CI of geometric mean ratios were within the range of 0.8 and 1.25 (Table 32). A high-fat meal shortens the median T_{max} of naproxen by approximately 30 minutes. However, the clinical significance of this shortening is unclear.

Table 32. Statistical Analysis of Food Effect on PK of Naproxen in Study RB5-US-1505

PK Parameters	Treatment A (Proposed Drug Product in Fasted Condition)[a] Geometric LSM	Treatment B (Proposed Drug Product in Fed Condition)[b] Geometric LSM	Fed/Fasted Ratio [Percentage (90% CI)] (N=70)
C_{max} (ng/mL)	36166.176	32635.701	90.23 (86.18-94.48)
AUC_{0-96h} (ng.h/mL)	624718.74	606639.19	97.11 (93.38-100.98)
AUC_{inf} (ng.h/mL)	653365.3	629009.61	96.27 (91.95-100.78)

Source: FDA Analysis using ADPC.xpt from Study RB5-US-1505
[a] The reference arm is the proposed drug product fasted condition (Treatment A: two Mucinex 12 HR Cold & Fever Multi-Symptom tablets after 10-hour fast.
[b] The test arm is the proposed drug product fed condition (Treatment B: two Mucinex 12 HR Cold & Fever Multi-Symptom tablets followed by a high fat standardized meal prior to which subjects fasted for 10 hours overnight).
Abbreviations: AUC_{inf}, area under the concentration-time curve estimated to infinity; AUC_{0-96h}, area under the concentration-time curve from time 0 to 96 hours; C_{max}, maximum plasma concentration; h, hour; LSM, least squares mean; mL, milliliter; N, number (of population); ng, nanogram; PK, pharmacokinetic

14.2.2. Summary of Clinical PK Findings in Pilot Study 2009-GGE-TRI-DM

Study 2009-GGE-TRI-DM was a Phase 1, open label, single dose, randomized, four-way crossover relative BA study of two experimental combination extended-release (ER) formulations of 600 mg guaifenesin, 220 mg naproxen sodium, and 60 mg dextromethorphan HBr under fasted and fed conditions compared to a combination of reference products under fasted conditions.

The primary objective of this study was to characterize the single-dose PK of two test formulations that include naproxen sodium, guaifenesin, and dextromethorphan in ER formulations administered under fasted conditions compared to a combination of reference products in healthy adults. The secondary objectives of this study were: 1) to determine whether

there is an effect on the PK properties of one of the test formulations when administered with food and 2) to determine the safety and tolerability of the test formulations in healthy adults.

Subjects were assigned to the following treatments in a crossover design keeping at least 10 days wash out period:

- Treatment A: Subjects received test formulation A (b) (4) after an overnight fast.
- Treatment B: Subjects received test formulation B (b) (4) after an overnight fast.
- Treatment C: Subjects received test formulation A (b) (4) 30 minutes after the beginning of the consumption of a high-fat FDA standardized meal.
- Treatment D (listed drug arm): Subjects received one 600 mg Mucinex, one 220 mg Aleve (200 mg naproxen), and one dose of 1 x 15 mL Vicks Formula 44 Custom Care Dry Cough Suppressant Syrup (30 mg/15 mL dextromethorphan q6h for 1 dose) taken at Hour 0, administered with 240 mL of water after an overnight fast, and 1 dose of 1 x 15 mL Vicks Formula 44 Custom Care Dry Cough Suppressant Syrup (30 mg/15 mL dextromethorphan q6h for 1 dose) taken at Hour 6 with 240 mL of water (also fasted).

Key Results From the Pilot Study

The study results showed that for guaifenesin, neither of the two test formulations was bioequivalent to the reference product for C_{max}, AUC_{0-t}, or AUC_{inf} under both fasted and fed conditions. Both test formulations under fasted conditions had lower values than the reference. Test A formulation under fed conditions was also not bioequivalent to the reference and had lower values for C_{max}, AUC_{0-t}, or AUC_{inf}. C_{max} was higher for Test A formulation fed compared to Test A formulation fasted, indicating a food effect. For naproxen and dextromethorphan, both test formulations were bioequivalent to the reference for AUC_{0-t}, or AUC_{inf}, but not bioequivalent for C_{max}. There was no food effect observed for the Test A formulation, but C_{max} was lower for the Test A formulation fed compared to the reference. For dextromethorphan, both test formulations under fasted conditions were bioequivalent to the reference for AUC_{0-t}, or AUC_{inf}, but not bioequivalent for C_{max}. Using the outcomes from this study, Test A formulation (fast release formulation) was further modified to address the food effect and the modified formulation was the formulation used in the Study RB5-US-1505.

14.3. Bioanalytical Method Validation and Performance

For bioanalysis of the PK samples from the pivotal BA/BE Study RB-US-1505, a high performance liquid chromatography-tandem mass spectrometry assay was used. This method can simultaneously determine the concentration of dextromethorphan, guaifenesin, and naproxen in K_2EDTA human plasma. It was developed and validated with study protocol (b) (4) Study Number: 1375-1902.[5,6,7] A solid phase extraction method was used. A total of 9,401 primary samples and 121 backup samples were analyzed in 176 runs within established storage period for three active ingredients.

The method validation summary and in study method performance are provided in Table 33 and Table 34, respectively.

Table 33. Summary of Method Validation for the Determination of Dextromethorphan, Guaifenesin, and Naproxen in Human Plasma in Study RB5-US-1505

Study Information	**Method Validation Summary**		
Report Title	Validation of a Method for the Determination of Dextromethorphan, Guaifenesin, and Naproxen in Human Plasma by LC-MS/MS		
Study Number	(b) (4) 1375-1902		
Analyte Name	***Dextromethorphan***	***Guaifenesin***	***Naproxen***
Internal Standard	Dextromethorphan-*d*3	Guaifenesin-*d*3	Naproxen-*d*3
Sample Volume	100 mL	100 mL	100 mL
QC Concentrations	0.01, 0.03, 0.4, 4, and 8 ng/mL	5, 15, 200, 2000, and 4000 ng/mL	50, 150, 2000, 20000, 40000 ng/mL
Standard Curve Concentrations	0.01, 0.02, 0.1, 0.3, 1, 3, 9, and 10 ng/mL	5, 10, 50, 150, 500, 1500, 4500, and 5000 ng/mL	50, 100, 500, 1500, 5000, 15000, 45000, and 50000 ng/mL
Lower Limit of Quantitation	0.01 ng/mL	5 ng/mL	50 ng/mL
Upper Limit of Quantitation	10 ng/mL	5000 ng/mL	50000 ng/mL
Mean Recovery of Analyte (%)	102.9	97.4	96.2
Mean Recovery of Internal Standard (%)	103.2	96.5	95.6
Variation of Matrix Effect from Six Lots of Matrix (%CV)	≤2.7	≤ 1.4	≤ 2.8
Sensitivity	The accuracy at LLOQ was within ±20.0% of their nominal values. The %CV at LLOQ was less than 20.0%		
LLOQ QC Intra-Run Precision Range (%CV)	3.9 to 8.0	2.8 to 5.6	3.5 to 5.2
LLOQ QC Intra-Run	4.0 to 11.0	-3.0 to 7.0	-1.8 to 5.8

[5] \\CDSESUB1\EVSPROD\nda217338\0003\m5\53-clin-stud-rep\531-rep-biopharm-stud\5314-bioanalyt-analyt-met\1375-1902\1375-1902.pdf

[6] \\CDSESUB1\EVSPROD\nda217338\0003\m5\53-clin-stud-rep\531-rep-biopharm-stud\5314-bioanalyt-analyt-met\1375-1902\1375-1902-amend-1.pdf

[7] \\CDSESUB1\EVSPROD\nda217338\0003\m5\53-clin-stud-rep\531-rep-biopharm-stud\5314-bioanalyt-analyt-met\1375-1902\1375-1902-amend-2.pdf

Study Information	Method Validation Summary		
Accuracy Range (%RE)			
Analytical QC Intra-Run Precision Range (%CV)	0.8 to 2.4	0.7 to 2.7	1.1 to 3.8
Analytical QC Intra-Run Accuracy Range (%RE)	-3.3 to 5.5	-5.3 to 4.5	-4.8 to 6.7
LLOQ QC Inter-Run Precision (%CV)	6.3	5.7	5.3
LLOQ QC Inter-Run Accuracy (%RE)	6.0	2.0	2.6
Analytical QC Inter-Run Precision Range (%CV)	1.4 to 2.2	1.3 to 2.3	2.5 to 3.1
Analytical QC Inter-Run Accuracy Range (%RE)	-2.4 to 4.0	-4.8 to 3.3	-4.3 to 6.0
Stock Solution Stability in Ethanol	121 Days at -20°C, 6 Hours at Ambient Temperature	126 Days at -20°C; 20 Hours at Ambient Temperature	126 Days at -20°C; 20 Hours at Ambient Temperature
Processed Sample Stability	148 Hours at 4°C		
Benchtop Stability in Plasma	19 Hours in an Ice Bath		
Freeze/Thaw Stability in Plasma	5 Cycles at -20°C and -70°C (thawed in an ice bath)		
Benchtop Stability in Whole Blood	2 Hours in an Ice Bath (centrifuged at 4°C and at ambient temperature)		
Long-term Storage Stability in Plasma	776 Days at -20°C and -70°C		
Dilution Integrity	60 ng/mL diluted 50-fold	10000 ng/mL diluted 50-fold	100000 ng/mL diluted 50-fold
Selectivity	The six lots of individual blank matrix met the acceptance criteria of: No interference peak area at the retention time of the peak for dextromethorphan, guaifenesin, and naproxen that was >20.0% of the mean analyte peak area of the lowest calibration standards and No interference peak area at the retention time of the IS that was >5.0% of the mean internal standard.		
Spike-in Selectivity (at LLOQ for 6 batches)	Precision: CV% (6.4) Accuracy: RE% (-9.9)	Precision: CV% (2.4) Accuracy: RE% (-10.4)	Precision: CV% (10.7) Accuracy: RE% (-4.8)
2% Hemolyzed Plasma Test[8]	No impact on assay performance		
Lipemic Plasma Test[9]	No impact on assay performance		
Batch Size Test	159 Injections		
Carryover[10]	<20% LLOQ (Dextromethorphan) <5% Carryover IS (Dextromethorphan-*d*3)	<20% LLOQ (Guaifenesin) <5% Carryover IS (Guaifenesin-*d*3)	<20% LLOQ (Naproxen) <5% Carryover IS (Naproxen-*d*3)

Source: NDA 217338; Bioanalytical method validation report; (Protocol # 1375-1902)
Abbreviations: C, Celsius; %CV, coefficient of variation; IS, internal standard; LC-MS/MS, liquid chromatography with tandem mass spectrometry; LLOQ, lower limit of quantification; mL, milliliter; ng, nanogram; QC, quality control; %RE, relative error

[8] NDA 217338; Bioanalytical method validation report; (Protocol # 1375-1902); Table 21-23
[9] NDA 217338; Bioanalytical method validation report; (Protocol # 1375-1902); Table 26-28
[10] NDA 217338; Bioanalytical method validation report; (Protocol # 1375-1902); Table 30-32

Table 34. Summary of In-Study Performance of LC-MS/MS Method for the Determination of Dextromethorphan, Guaifenesin, and Naproxen in Human Plasma in Study RB5-US-1505

Performance Parameters	Results
Assay Passing Rate	• *Dextromethorphan:* 97 of 103 runs (94.2%) met acceptance criteria, including ISR runs. Three runs were rejected, and three runs were aborted. • *Guaifenesin:* 85 of 88 runs (96.6%) met acceptance criteria, including incurred sample reanalysis. One run was rejected, and two runs were aborted. • *Naproxen:* 82 of 84 runs (97.6%) met acceptance criteria, including ISR runs. No runs were rejected, and two runs were aborted.
Standard Calibration Curve	• *Dextromethorphan:* 8 calibration standards from 0.01 to 10 ng/mL • *Guaifenesin:* 8 calibration standards from 5 to 5000 ng/mL • *Naproxen:* 8 calibration standards from 50 to 50000 ng/mL
Standard Calibration Performance	• *Dextromethorphan:* Cumulative bias range: -2.3% to 3.0% • *Guaifenesin:* Cumulative bias range: -2.2% to 2.2% • *Naproxen:* Cumulative bias range: -2.7% to 2.6% • *Dextromethorphan:* Cumulative precision: □5.9% CV • *Guaifenesin:* Cumulative precision: □6.6% CV • *Naproxen:* Cumulative precision: □5.0% CV
QC Performance	• *Dextromethorphan:* Cumulative bias range: -0.5% to 3.3% • *Guaifenesin:* Cumulative bias range: -0.8% to 3.0% • *Naproxen:* Cumulative bias range: -0.8% to 3.5% • *Dextromethorphan:* Cumulative precision: □6.8% CV • *Guaifenesin:* Cumulative precision: □6.9% CV • *Naproxen:* Cumulative precision: □6.6% CV
Method Reproducibility	• *Dextromethorphan:* ISR was performed in 530 (5.6%) of 9522 analyzed study samples, and 80.9% met the pre-specified acceptance criteria. • *Guaifenesin:* ISR was performed in 536 (5.6%) of 9522 analyzed study samples, and 93.1% met the pre-specified acceptance criteria. • *Naproxen:* ISR was performed in 550 (5.8%) of 9522 analyzed study samples, and 93.3% met the pre-specified acceptance criteria.
Sample analysis and storage time	A total of 9522 samples were analyzed within established long term storage time (776 Days at -20°C and -70°C). The first sample collection date was December 8, 2021, and last sample analysis date was December 14, 2022 (372 days).

Source: Study RB5-US-1505: Bioanalytical Sample Analysis Report[11]
Abbreviations: C, Celsius; CV, coefficient of variation; ISR, incurred sample reanalysis; LC-MS/MS, liquid chromatography with tandem mass spectrometry; QC, quality check

[11] \\CDSESUB1\EVSPROD\nda217338\0003\m5\53-clin-stud-rep\531-rep-biopharm-stud\5314-bioanalyt-analyt-met\1375-1903\1375-1903.pdf

14.4. Immunogenicity Assessment—Impact of PK/PD, Efficacy, and Safety

Not applicable.

14.5. Pharmacometrics Assessment

Physiological-Based Pharmacokinetic Modeling

Executive Summary

This review evaluates the adequacy of the Applicant's physiological-based pharmacokinetics (PBPK) analysis to simulate the PK of dextromethorphan, guaifenesin, and naproxen, following administration of the proposed bilayer product in adolescents (subjects aged 12 to 17 years).

Based on the review of the Applicant's PBPK modeling submission (report RECK-5b and modeling and simulations files), the Division of Pharmacometrics concluded that the PBPK analysis was inadequate to support extrapolation of adult PK data to adolescents. The analysis was not sufficiently developed and verified for its intended purpose.

(b) (4)

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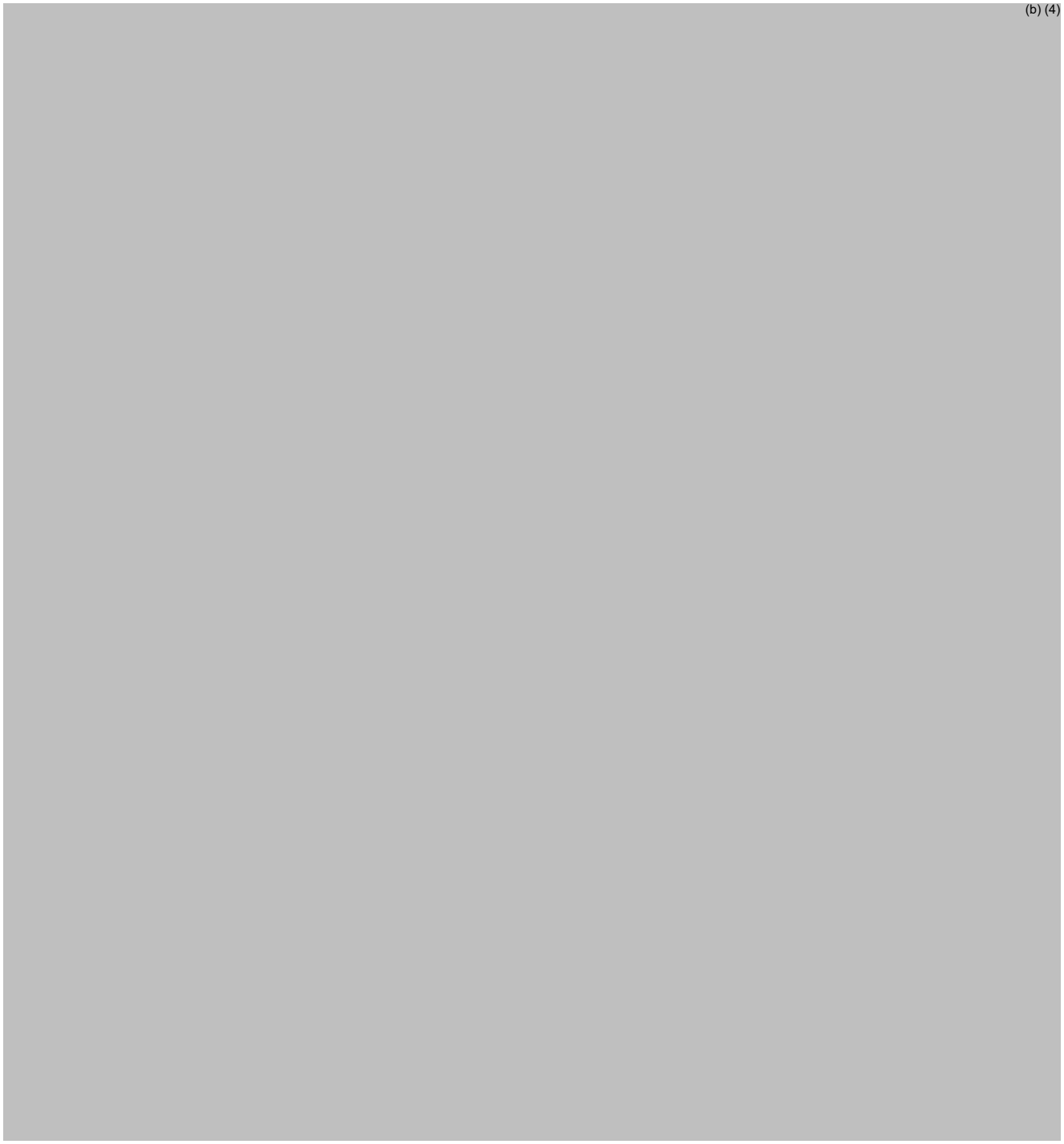


14.6. Pharmacogenetics

Not applicable.

15. Study/Trial Design

Not applicable.

16. Efficacy

Not applicable.

17. Clinical Safety

RB Heath conducted two exploratory Phase 1 PK studies of early versions of the fixed dose combination product before development of the final to-be-marketed formulation. These early studies were conducted with formulations that are different from the current proposed fixed dose combination product. Nonetheless, because they used a combination of the three active ingredients– guaifenesin, dextromethorphan, and naproxen – the clinical safety data generated from the two studies are reviewed for completeness.

17.1. Study 2009-GGE-TRI-DM

This was a Phase 1, open-label, randomized, single-dose, four-way crossover, relative BA study of two experimental combination ER formulations (b) (4) comprising 600 mg guaifenesin, 60 mg dextromethorphan and 220 mg naproxen sodium evaluated under fasted and fed conditions.

Investigational Products:

- Test A - (b) (4) formulation of an ER bilayer tablet containing 600 mg Mucinex, 60 mg dextromethorphan, and 220 mg naproxen sodium
- Test B - (b) (4) formulation of an ER bilayer tablet containing 600 mg Mucinex, 60 mg dextromethorphan, and 220 mg naproxen sodium
- Reference drug - an ER bilayer tablet containing one 600 mg Mucinex, one 220 mg Aleve (200 mg naproxen), and a 15 mL dose of Vicks Formula 44 Custom Care Dry Cough Suppressant Syrup (30 mg/15 mL of dextromethorphan)

Primary Objectives

To characterize the single dose PK for two test formulations that include the three active ingredients in ER formulations administered under fasted conditions compared to a combination of listed products in healthy adults.

Secondary Objectives

To determine whether there is an effect on the PK properties of one of the test formulations when administered with food and to determine the safety and tolerability of the test formulations in healthy adults.

Safety Results

In this study, a total of 30 subjects were randomized to participate. Twenty-seven subjects completed all four study treatments. There were two discontinuations in this study. One subject was discontinued due to having streptococcal pharyngitis requiring antibiotics. A second subject was discontinued due to a positive screening test for amphetamines.

Seven subjects (7/30, 23%) reported a total of 16 TEAEs. All adverse events (AEs) were mild and resolved without complications by the end of study. There were no deaths or serious adverse events. In Table 41 below, the Applicant presented the TEAEs that were reported by greater than 1 subject. Nausea, dizziness and headache were reported by 2 subjects each. All remaining TEAEs were reported by one subject each.

Table 41. Incidence of Treatment-Emergent Adverse Events Overall and Events Reported by More Than One Subject

Adverse Event	Treatment				Overall
	A	B	C	D	
Number of subjects dosed	N = 28	N = 27	N = 29	N = 29	N = 30
Number of subjects reporting any TEAE	4 (14%)	3 (11%)	1 (3%)	2 (7%)	7 (23%)
Number of subjects reporting nausea	2 (7%)	1 (4%)	0	0	2 (7%)
Number of subjects reporting dizziness	1 (4%)	0	1 (3%)	0	2 (7%)
Number of subjects reporting headache	2 (7%)	1 (4%)	0	1 (3%)	2 (7%)
Treatment A (Test A fasted) = 1 x 600 mg Mucinex®, 220 mg naproxen sodium (200 mg naproxen), and 60 mg dextromethorphan - Test A (fasted) Treatment B (Test B fasted) = 1 x 600 mg Mucinex®, 220 mg naproxen sodium (200 mg naproxen), and 60 mg dextromethorphan - Test B (fasted) Treatment C (Test A fed) = 1 x 600 mg Mucinex®, 220 mg naproxen sodium (200 mg naproxen), and 60 mg dextromethorphan - Test A (fed) Treatment D (Reference fasted) = 1 x 600 mg Mucinex®, 1 x 220 mg Aleve (200 mg naproxen), and 1 x 15 mL (30 mg) dextromethorphan syrup at Hour 0, plus 1 x 15 mL (30 mg) dextromethorphan syrup at Hour 6 (fasted)					

Source: eCTD Module 2.7.4 Summary of Clinical Safety, Table 40
Abbreviations: mg, milligram; mL, milliliter; N, number (of population); TEAE, treatment-emergent adverse event

Conclusion

Few AEs were generally noted in this study. AEs were all noted to be mild and self-limited. The preferred terms reported were overall similar to those reported from the pivotal study. These results did not alter the safety conclusions for this combination product.

17.2. Study 2014-MUCDM-02

This was a Phase 1, open label, randomized, single-dose, five-period, five-sequence, crossover relative BA study of two experimental combination ER formulations comprising 600 mg guaifenesin, 30 mg dextromethorphan, and 110 mg naproxen sodium evaluated under fasted and fed conditions.

Investigational Products:

- Two (b) (4) each containing an ER bilayer tablet with 600 mg guaifenesin, 30 mg dextromethorphan, and (b) (4) 110 mg of naproxen sodium
- Two (b) (4) each containing an ER bilayer tablet with 600 mg guaifenesin, 30 mg dextromethorphan, and (b) (4) 110 mg of naproxen sodium
- Reference drug- Two Mucinex DM ER bilayer tablets (600 mg guaifenesin, 30 mg dextromethorphan) and one Aleve tablet (220 mg naproxen sodium)

Primary Objectives

- To characterize the single dose PK for two test ER formulations containing guaifenesin, dextromethorphan, and naproxen sodium when administered under fasted conditions, and compared to a combination of listed products administered under fasted conditions in healthy adults
- To determine if there is an effect on the PK properties of the two test formulations when administered with food

Secondary Objectives

To determine the safety and tolerability of the test formulations in healthy adults.

Safety Results

A total of 25 subjects participated in this study. Nine subjects (9/25; 36%) experienced a total of 21 AEs. All AEs were considered mild in severity. One subject was discontinued due to protocol deviation of using a caffeine containing beverage. There were no deaths or serious adverse events. Table 42 indicated all Applicant-provided TEAEs reported. Generally, the numbers associated with any one AE are very small. The AEs with the greatest number of reports were feeling of relaxation (n=3), hemoglobin decrease (n =3), headache (n=2), and diarrhea (n=2).

Table 42. Summary of Adverse Events by Body System and MedDRA Term

		Treatment A		Treatment B		Treatment C		Treatment D		Treatment E	
SOC	PT	Subjects	Events	Subjects	Events	Subjects	Events	Subjects	Events	Subjects	Events
Eye Disorders											
	Eye Pruritus	0	0	0	0	1	1	0	0	0	0
	Eyelid Edema	0	0	0	0	0	0	1	1	0	0
	Ocular Hyperemeia	0	0	0	0	1	1	0	0	0	0
Gastrointestinal Disorders											
	Abdominal Pain	0	0	1	1	0	0	0	0	0	0
	Abdominal Pain, upper	0	0	0	0	0	0	1	1	0	0
	Diarrhea	0	0	0	0	0	0	0	0	2	2
	Nausea	1	1	0	0	0	0	0	0	0	0
General Disorders											
	Feeling of relaxation	1	1	1	1	0	0	0	0	1	1
	Vessel Puncture Site Pain	0	0	1	1	0	0	0	0	0	0
	Vessel Puncture Site Swelling	0	0	0	0	0	0	0	0	1	1
Investigations											
	Hemoglobin Decreased	0	0	1	1	1	1	0	0	1	1
Musculoskeletal and											
Connective Tissue	Muscle Spasms	0	0	1	1	0	0	0	0	0	0
Disorders	Pain in Extremity	0	0	0	0	0	0	0	0	1	1
Nervous System Disorders											
	Headache	1	1	1	1	0	0	0	0	0	0
Skin and Subcutanous											
Tissue Disorders	Pruritus	0	0	1	1	0	0	0	0	0	0

Source: Generated by reviewer. Adapted from eCTD, Module 2.7.4, Summary of Clinical Safety Table 41
Treatment A: two (b) (4) ER bilayer tablet with 600 mg guaifenesin, 30 mg dextromethorphan, and (b) (4) 110 mg of naproxen sodium under fasted condition
Treatment B: two (b) (4) ER bilayer tablet with 600 mg guaifenesin, 30 mg dextromethorphan, and (b) (4) 110 mg of naproxen sodium under fed condition
Treatment C: two (b) (4) ER bilayer tablet with 600 mg guaifenesin, 30 mg dextromethorphan, (b) (4) 110 mg of naproxen sodium under fasted condition
Treatment D: ER bilayer tablet with 600 mg guaifenesin, 30 mg dextromethorphan, and (b) (4) 110 mg of naproxen sodium under fed condition
Treatment E: two Mucinex DM (600 mg guaifenesin, 30 mg dextromethorphan) ER bilayer tablet and one Aleve table (200 mg naproxen sodium) under fasted condition
Abbreviations: MedDRA, Medical Dictionary for Regulatory Activities; mg, milligram; PT, preferred term; SOC, system organ class

Conclusion

There were no significant safety findings noted in this exploratory study. The preferred terms reported were generally similar to those reported from the pivotal study. AEs were noted to be mild and self-limited. The results did not alter the safety conclusions for this combination product.

18. Clinical Virology

Not applicable.

19. Clinical Microbiology

Not applicable.

20. Mechanism of Action/Drug Resistance

Not applicable.

21. Other Drug Development Considerations

Not applicable.

22. Data Integrity–Related Consults (Office of Scientific Investigations, Other Inspections)

Not applicable.

23. Labeling: Key Changes and Considerations

23.1. Approved Labeling Types

Label negotiations have not been performed for this NDA submission. This submission is expected to conclude with a complete response letter due to the deficiencies noted in other sections. For a complete list of deficiencies, refer to Section 2.

23.2. Approach to the Labeling Review

The proposed draft labeling for guaifenesin, dextromethorphan HBr, and naproxen sodium ER tablets was assessed to determine whether it was presented in accordance with all applicable regulations. The proposed Drug Facts label (DFL) closely mirrors the approved DFL for Aleve tablets (NDA 020204) and Mucinex DM ER tablets (NDA 021620). Most of the review issues identified for the proposed labeling are related to the proposed principal display panel (PDP) and the accuracy of the proprietary name.

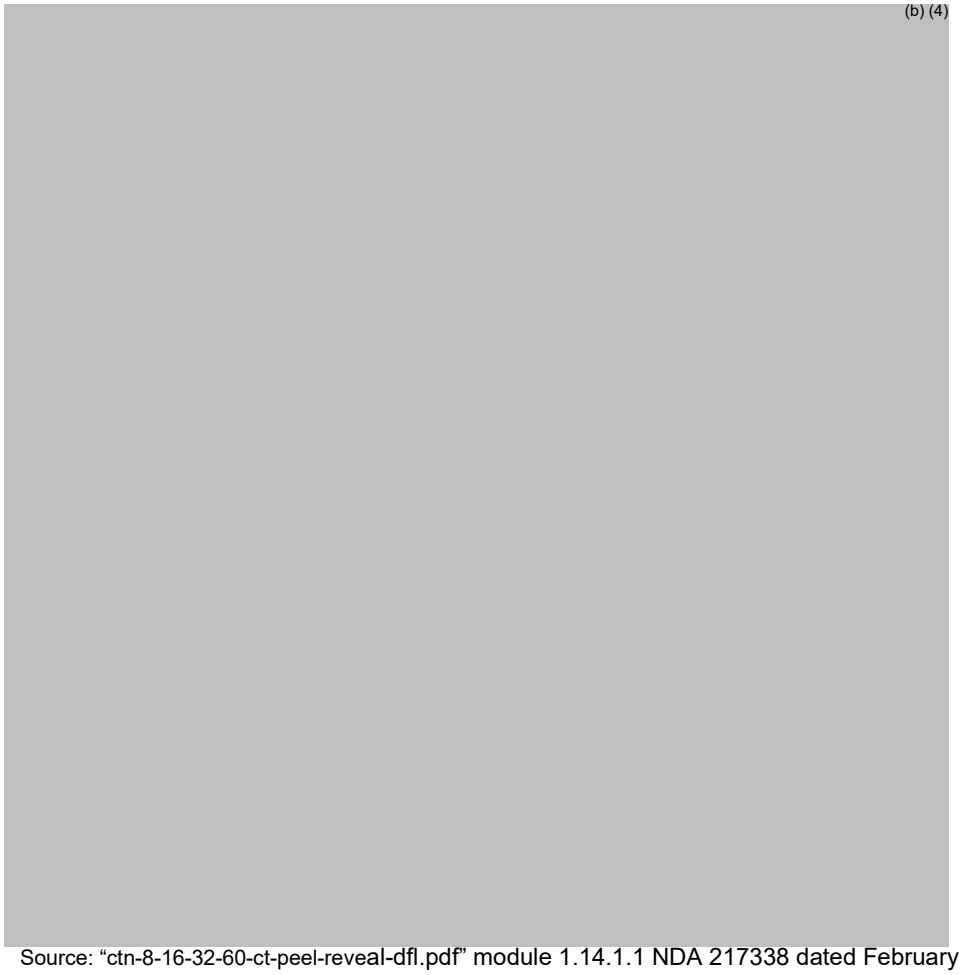
Table 43. Proposed Draft Labeling

Proposed Label	Date Submitted
4-count Outer Carton (HCP sample)	September 29, 2023, February 22, 2024
4-count Blister Mat (HCP sample)	September 29, 2023, February 22, 2024
4-count Outer Carton Peel-Back DFL	September 29, 2023, February 22, 2024
8-count Outer Carton	September 29, 2023, February 22, 2024
8-count Blister Mat	September 29, 2023, February 22, 2024
16-count Outer Carton	September 29, 2023, February 22, 2024
32-count Outer Carton	September 29, 2023, February 22, 2024
60-count Outer Carton	September 29, 2023, February 22, 2024
10-count Blister Mat	September 29, 2023, February 22, 2024
8-, 16-, 32-, 60-count Outer Carton Peel-Back DFL	September 29, 2023, February 22, 2024

Source: Reviewer generated table using labeling materials from NDA Module 1.14.1.1 submitted September 29, 2023, and February 22, 2024
Abbreviations: DFL, Drug Facts label; HCP, health care professional

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

(b) (4)



Source: "ctn-8-16-32-60-ct-peel-reveal-dfl.pdf" module 1.14.1.1 NDA 217338 dated February 22, 2024
Abbreviations: C, Celsius; F, Fahrenheit; FD&C, Food, Drugs, & Cosmetics; HBr, hydrobromide; HR, hour; mg, milligram; MAOI, monoamine oxidase inhibitor; NJ, New Jersey; NSAID, nonsteroidal anti-inflammatory drug; US, United States

As mentioned in the section above, the proposed DFL closely follows the approved DFL for Mucinex DM ER tablets (NDA 021620) and Aleve tablets (NDA 020204). The following substantive issues to the proposed DFL have been identified:

- The DFL references tablets; however, the product is an ER tablet. The dosage form should be revised from *tablet* to *extended-release tablet* throughout the DFL.
- Similar products contain directions for dosing with regard to the timing of meals. The Applicant should address that issue for this product and update the DFL as needed.

Annotation on the labeling files indicates that the labeling meets the print/formatting requirements from 21 CFR 201.66(d). As this product contains sodium above 5 mg per dosage unit, its labeling is required to include a description of the sodium content as described in 21 CFR 201.64. The proposed labeling complies with this regulation.

23.3.2. Principal Display Panel and Side Panels

In the original submission dated October 6, 2023, the Applicant submitted a different proposed proprietary name, (b) (4). After reviewing the currently approved indications for the three active ingredients, it was determined that none of the active ingredients (b) (4) The Division of Medication Error Prevention and Analysis held a teleconference with the Applicant 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 do not include (b) (4) (b) (4) (b) (4). On December 11, 2023, the Applicant withdrew the proposed proprietary name, (b) (4). The Applicant 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 (see Section 6.3.1 for more details).

Figure 8. Proposed PDP

(b) (4)

Source: "ctn-8-ct-ctn.pdf," module 1.14.1.1 NDA 217338 dated February 22, 2024
Abbreviations: HBr, hydrobromide; HR, hour; mg, milligram; NSAID, nonsteroidal anti-inflammatory drug; PDP, Principal Display Panel

The following concerns have been identified for the PDP:

- The font size for the proprietary name is not consistent. The Applicant has chosen to use three different font sizes with "Mucinex" in the largest font size, "12HR Cold & Fever" in a smaller font size, and "Multi-Symptom" in the smallest font size. We recommend the entire proprietary name be in the same font size. However, if the current brand name size is maintained, we strongly recommend the font size for "12HR Cold & Fever" and "Multi-Symptom" be in the same font size.
- The font size for the statement of identity (SOI) is 25% of the largest font on the PDP. This is the minimum acceptable font size; however, it is hard to read relative to the largest font and we recommend it be increased.
- The SOI is missing the dosage form. We recommend that "extended-release tablets" be added to the SOI.
- The SOI should be in bold face type as required by 21 CFR 201.61.
- The clock image on the PDP has 12HR in the middle of the image (b) (4). We recommend the clock (b) (4) have 12 ticks to be consistent with the proposed labeled duration of use.
- The PDP includes a tablet image. The tablet should be an actual representation of the tablet and should be labeled "actual size."
- On the 32-count and 60-count labeling, the proprietary name is presented on the top panel as:

  Mucinex
  12HR Cold & Fever
  Multi-Symptom
  (b) (4)

  The addition of (b) (4)" directly adjacent to the proprietary name is unacceptable. While the statement (b) (4)" is acceptable to the labeling review team, placing it directly adjacent to the approved proprietary name implies it is part of the proprietary name. The (b) (4)" statement needs to be placed elsewhere on the top panel.

23.3.3. Immediate Container (Blister Mat) Labeling

The Applicant submitted immediate container (blister mat) labeling. Three proposed blister mat labels were submitted, 4-, 8- and 10-count blister mats. These blister mats contain the tablets in individual blisters. Each blister has a unique back label which contains important information to the consumer. The proposed back label of the blister mats contains the following information: proposed proprietary name, SOI, distributor information, the nonsteroidal anti-inflammatory drug (NSAID) stomach bleeding warning, and the warning to "Keep this warning. Do not detach individual blisters until ready to use." The panels of the blister mats listing the brand name and SOI, also include a warning, "See warnings before use." The NSAID stomach bleeding warning, which is on the Aleve NDA 20204 DFL reads:

Stomach bleeding warning: This product contains an NSAID, which may cause severe stomach bleeding. The chance is higher if you:

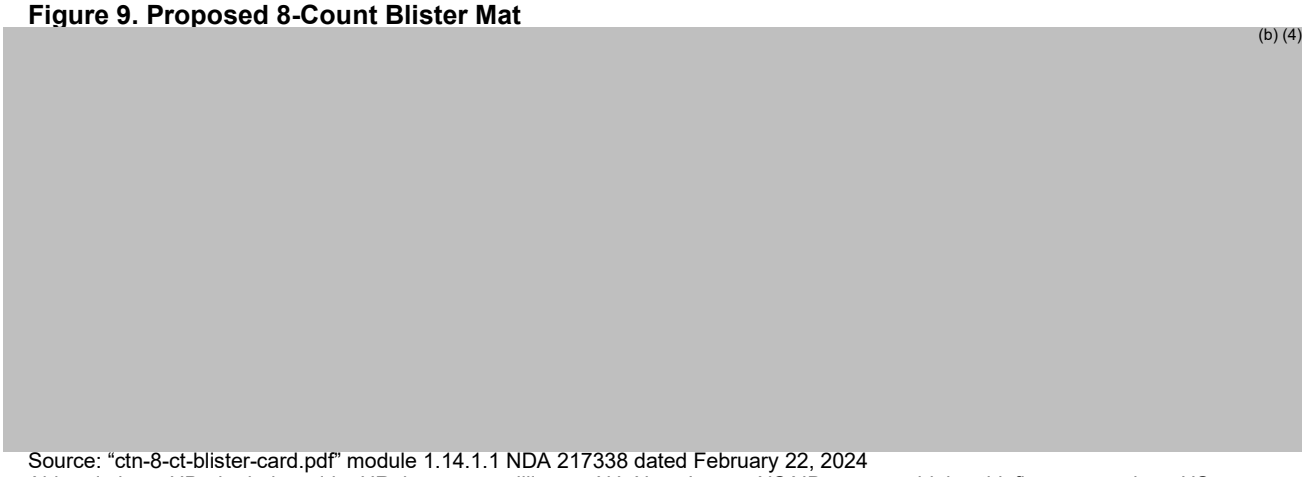
- Are age 60 or older

- 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

These warnings are on blisters that do not contain tablets, so the warnings will remain intact after each tablet is removed from the blister mat. The consumer will continue to have access to the warnings in case the outer carton is thrown away.

Figure 9. Proposed 8-Count Blister Mat

(b) (4)



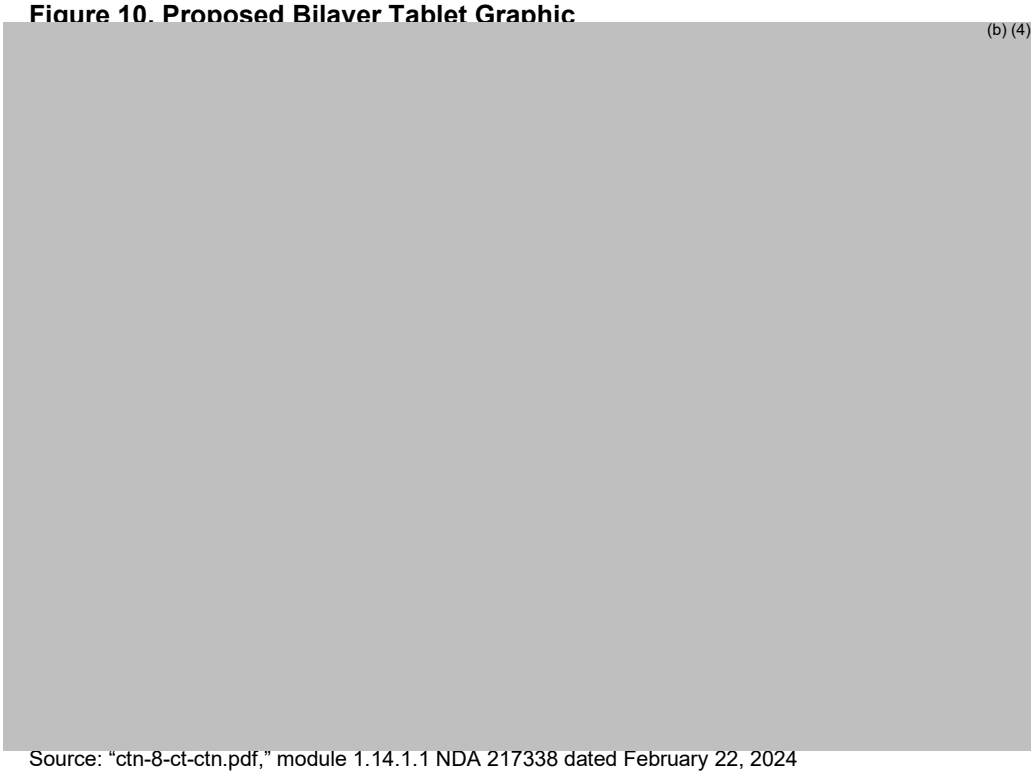
Source: "ctn-8-ct-blister-card.pdf" module 1.14.1.1 NDA 217338 dated February 22, 2024
Abbreviations: HBr, hydrobromide; HR, hour; mg, milligram; NJ, New Jersey; NSAID, nonsteroidal anti-inflammatory drug; US, United States

23.4. Review Issues

- The font size for the proprietary name is not consistent. The Applicant has chosen to use three different font sizes with "Mucinex" in the largest font size, "12HR Cold & Fever" in a smaller font size, and "Multi-Symptom" in the smallest font size. We recommend the proprietary name be in the same font size. However, we acknowledge that it is common for the brand name to be in the largest font. If this is maintained, we strongly recommend the font size for "12HR Cold & Fever" and "Multi-Symptom" be in the same font size.
- The font size for the SOI is 25% of the largest font on the PDP. This is the minimum acceptable font size; however, it is hard to read relative to the largest font and we recommend it be increased.
- The SOI is missing the dosage form. We recommend that "extended-release tablets" be added to the SOI.
- The SOI should be in bold face type as required by 21 CFR 201.61.

- The clock image on the PDP has 12HR in the middle of the image (b) (4). We recommend the clock (b) (4) have 12 ticks to be consistent with the proposed labeled duration of use.
- The PDP includes a tablet image. The tablet should be an actual representation of the tablet and should be labeled "actual size" (see Figure 11 for the location of the bilayer tablet graphic image)

Figure 10. Proposed Bilayer Tablet Graphic



Source: "ctn-8-ct-ctn.pdf," module 1.14.1.1 NDA 217338 dated February 22, 2024

- On the 32-count and 60-count labeling (see Figure 12), the proprietary name is presented on the top panel as:

Mucinex
12HR Cold & Fever
Multi-Symptom
(b) (4)

The addition of "(b) (4)" directly adjacent to the proprietary name is unacceptable. While the statement "(b) (4)" is acceptable to the labeling review team, placing it directly adjacent to the approved proprietary name implies it is part of the proprietary name. The "(b) (4)" statement needs to be placed elsewhere on the top panel.

Figure 11. Proposed Top Panel Bilayer Tablet Graphic Representing 32-Count and 60-Count

Source: "ctn-32-ct-ctn.pdf," module 1.14.1.1 NDA 217338 dated February 22, 2024
Abbreviation: HR, hour

Figure 12. Proposed Top Panel Bilayer Tablet Graphic Representing 4-Count, 8-Count, and 16-Count Cartons

Source: "ctn-8-ct-ctn.pdf," module 1.14.1.1 NDA 217338 dated February 22, 2024

- The DFL references "tablets"; however, the product is an ER tablet. The dosage form should be revised from *tablet* to *extended-release tablet* throughout the DFL.

23.5. Outstanding Items to Address During Label Negotiations

Label negotiations have not been performed for this NDA submission. This submission is expected to conclude with a complete response letter due to the deficiencies noted in other sections.

The labeling comments are being provided for completeness of the review. Given that the duration of action has not been established and therefore, directions for use are uncertain, we do not recommend these comments be provided to the Applicant at this time as the issues raised may change if the product changes.

24. Postmarketing Requirements and Commitments

Not applicable.

25. Financial Disclosure

Table 44. Covered Clinical Studies: RB5-US-1505

Was a list of clinical investigators provided:	Yes ☒☐	No ☐ (Request list from Applicant)
Total number of investigators identified: 12		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c), and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: Not applicable Significant payments of other sorts: Not applicable Proprietary interest in the product tested held by investigator: Not applicable Significant equity interest held by investigator: Not applicable Sponsor of covered study: Not applicable		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3): 12		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

Abbreviation: FDA, Food and Drug Administration

26. References

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27. Review Team

Table 45. Reviewers of Integrated Assessment

Role	Name(s)
Regulatory Project Manager	Tam Dinh
Chief of Project Management Staff	Daniel Brum
Nonclinical Reviewer	Chibueze Ihunnah
Nonclinical Team Leader	Donald Charles Thompson
OCP/DIIP Reviewer	Sanjida Mahjabeen
OCP/DIIP Team Leader	Yunzhao Ren
OCP/DPM PBPK Reviewer	Manuela Grimstein
OCP/DPM PBPK Team Leader	Yuching Yang
DAAP Clinical Reviewer	Timothy Jiang
DAAP Clinical Team Leader	Nancy Dickinson
DAAP Clinical Pharmacology	Srikanth C. Nallani
DAAP Clinical Pharmacology Team Leader	Deep Kwatra
Controlled Substance Staff	Chad Reissig
DNPD I Clinical Reviewer	Aklil Getachew
DNPD I Clinical Team Leader	Dorothy Chang
Labeling Reviewer	Michelle Walker
Labeling Team Leader	Steve Adah
CMC Application Technical Lead	Swapan De
CMC Supervisory Chemist	Danae Christodoulou
Cross-Disciplinary Team Leader DNPD I Clinical Team Leader	Dorothy Chang
Division director (DNPD I Clinical/Signatory)	Nushin Todd

Abbreviations: OB, Office of Biostatistics; OCP, Office of Clinical Pharmacology; DNPD I, Division of Nonprescription Drugs I

Table 46. Additional Reviewers of Application

Office or Discipline	Name(s)
DAAP Clinical	Alla Bazini
OPQ	Dhanalakshmi Kasi, Esther Jones, Stephanie Springer, Sithamalli Chandramouli, Suong Tran, Min Sung Suh, Kevin Wei
OSE/DMEPA	Ashleigh Lowery, Grace Jones, Abiola Olagundoye
IAMA	Rhonda Hearns-Stewart, Nikia Morris
Medical Editors	Monika Deshpande, Allison Cruz

Abbreviations: DAAP, Division of Anesthesiology, Addiction Medicine, and Pain Medicine; DEPI, Division of Epidemiology; DMEPA, Division of Medication Error Prevention and Analysis; DRISK, Division of Risk Management; IAMA, Integrated Assessment of Marketing Applications; OND, Office of New Drugs; OPDP, Office of Prescription Drug Promotion; OPQ, Office of Pharmaceutical Quality; OSE, Office of Surveillance and Epidemiology; OSI, Office of Scientific Investigations

27.1. Reviewer Signatures

See next page

Table 47. Signatures of Reviewers

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory	Consent To Include on Public List of Reviewers
Regulatory Project Management Regulatory Project Manager	Tam Dinh OND/ORO/DRO-NPD	☐ Benefit-Risk Assessment ☐ Interdisciplinary Assessment ☒ Additional Information and Analyses Sections: 12	Based on my assessment of the application: ☐ No deficiencies preclude approval. ☒ Deficiencies preclude approval. ☐ Not applicable.		☒ Yes ☐ No
Signature/date/time stamp: Tam Dinh -S Digitally signed by Tam Dinh -S Date: 2024.07.24 09:25:32 -04'00'					
Regulatory Project Management CPMS	Daniel Brum OND/ORO/DRO-NPD	☐ Benefit-Risk Assessment ☐ Interdisciplinary Assessment ☐ Additional Information and Analyses Sections: N/A (Suggested edits for clarity to multiple sections)	Based on my assessment of the application: ☐ No deficiencies preclude approval. ☒ Deficiencies preclude approval. ☐ Not applicable.		☒ Yes ☐ No
Signature/date/time stamp: Daniel Brum -S Digitally signed by Daniel Brum -S Date: 2024.07.26 13:21:26 -04'00'					

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory	Consent To Include on Public List of Reviewers
Clinical Pharmacology Secondary Reviewer	Yunzhao Ren OTS/OCP/DIIP	☐ Benefit-Risk Assessment ☐ Interdisciplinary Assessment ☐ Additional Information and Analyses Sections: 5,6.3,10,14	Based on my assessment of the application: ☐ No deficiencies preclude approval. ☒ Deficiencies preclude approval. ☐ Not applicable.		☒ Yes ☐ No
Signature/date/time stamp: Yunzhao Ren -S Digitally signed by Yunzhao Ren -S Date: 2024.07.23 16:33:52 -04'00'					
Clinical Pharmacology Reviewer	Sanjida Mahjabeen OTS/OCP/DIIP	☐ Benefit-Risk Assessment ☐ Interdisciplinary Assessment ☐ Additional Information and Analyses Sections: 5,6.3,10,14	Based on my assessment of the application: ☐ No deficiencies preclude approval. ☒ Deficiencies preclude approval. ☐ Not applicable.		☒ Yes ☐ No
Signature/date/time stamp: Sanjida Mahjabeen -S Digitally signed by Sanjida Mahjabeen -S Date: 2024.07.23 16:29:19 -04'00'					

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory	Consent To Include on Public List of Reviewers
Clinical Pharmacology Team Leader	Deep Kwatra OTS/OCP/DNP	☐ Benefit-Risk Assessment ☐ Interdisciplinary Assessment ☒ Additional Information and Analyses Sections: 6.3.1	Based on my assessment of the application: ☐ No deficiencies preclude approval. ☒ Deficiencies preclude approval. ☐ Not applicable.		☒ Yes ☐ No
Signature/date/time stamp: Deep Kwatra -S Digitally signed by Deep Kwatra -S Date: 2024.07.25 12:00:32 -04'00'					
Clinical Pharmacology Reviewer	Srikanth C. Nallani OTS/OCP/DNP	☐ Benefit-Risk Assessment ☐ Interdisciplinary Assessment ☒ Additional Information and Analyses Sections: 6.3.1	Based on my assessment of the application: ☐ No deficiencies preclude approval. ☒ Deficiencies preclude approval. ☐ Not applicable.		☒ Yes ☐ No
Signature/date/time stamp: Srikanth C. Nallani -S Digitally signed by Srikanth C. Nallani -S Date: 2024.07.25 11:35:22 -04'00'					

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory	Consent To Include on Public List of Reviewers
Clinical Team Leader	Dorothy Chang OND/ONPD/DNPDI	☒ Benefit-Risk Assessment ☒ Interdisciplinary Assessment ☒ Additional Information and Analyses Sections:	Based on my assessment of the application: ☐ No deficiencies preclude approval. ☒ Deficiencies preclude approval. ☐ Not applicable.		☒ Yes ☐ No
Signature/date/time stamp: Dorothy Chang -S Digitally signed by Dorothy Chang -S Date: 2024.07.26 13:25:39 -04'00'					
Clinical Reviewer	Aklil Getachew OND/ONPD/DNPDI	☒ Benefit-Risk Assessment ☒ Interdisciplinary Assessment ☒ Additional Information and Analyses Sections: 1,2,3,6.2,6.3,7.2,7.3,7.4,7.5,7.6,7.7,8,12,17	Based on my assessment of the application: ☐ No deficiencies preclude approval. ☒ Deficiencies preclude approval. ☐ Not applicable.		☒ Yes ☐ No
Signature/date/time stamp: Aklil Getachew -S Digitally signed by Aklil Getachew -S Date: 2024.07.26 09:18:35 -04'00'					

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory	Consent To Include on Public List of Reviewers
Clinical Team Leader	Nancy Dickinson OND/ON/DAAP	☐ Benefit-Risk Assessment ☒ Interdisciplinary Assessment ☐ Additional Information and Analyses Sections: 6.3.1	Based on my assessment of the application: ☐ No deficiencies preclude approval. ☒ Deficiencies preclude approval. ☐ Not applicable.		☒ Yes ☐ No
Signature/date/time stamp: Nancy C. Dickinson -S Digitally signed by Nancy C. Dickinson -S Date: 2024.07.25 09:35:55 -04'00'					
Clinical Reviewer	Timothy Jiang OND/ON/DAAP	☐ Benefit-Risk Assessment ☒ Interdisciplinary Assessment ☐ Additional Information and Analyses Sections: 6.3.1	Based on my assessment of the application: ☐ No deficiencies preclude approval. ☒ Deficiencies preclude approval. ☐ Not applicable.		☒ Yes ☐ No
Signature/date/time stamp: Timothy Jiang -S Digitally signed by Timothy Jiang -S Date: 2024.07.25 08:47:34 -04'00'					

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory	Consent To Include on Public List of Reviewers
Interdisciplinary Scientist Team Leader	Steven Adah OND/ONPD/DNPDI	☐ Benefit-Risk Assessment ☐ Interdisciplinary Assessment ☒ Additional Information and Analyses Sections: 23	Based on my assessment of the application: ☐ No deficiencies preclude approval. ☒ Deficiencies preclude approval. ☐ Not applicable.		☒ Yes ☐ No
Signature/date/time stamp: Michelle Walker signing on behalf of Steven Adah Michelle Walker -S Digitally signed by Michelle Walker -S Date: 2024.07.24 12:02:24 -04'00'					
Interdisciplinary Scientist Reviewer	Michelle Walker OND/ONPD/DNPDI	☐ Benefit-Risk Assessment ☐ Interdisciplinary Assessment ☒ Additional Information and Analyses Sections: 23	Based on my assessment of the application: ☐ No deficiencies preclude approval. ☒ Deficiencies preclude approval. ☐ Not applicable.		☒ Yes ☐ No
Signature/date/time stamp: Michelle Walker -S Digitally signed by Michelle Walker -S Date: 2024.07.24 12:01:44 -04'00'					

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory	Consent To Include on Public List of Reviewers
Product Quality Supervisory Chemist	Danae Christodoulou OPQOPQAII/IX	☐ Benefit-Risk Assessment ☐ Interdisciplinary Assessment ☐ Additional Information and Analyses Sections: 9	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.		☒ Yes ☐ No
Signature/date/time stamp: Danae D. Christodoulou -S Digitally signed by Danae D. Christodoulou -S Date: 2024.07.25 14:07:24 -04'00'					
Product Quality Senior Pharmaceutical Quality Assessor, Application Team Lead	Swapan De OPQOPQAII/IX	☒ Benefit-Risk Assessment ☐ Interdisciplinary Assessment ☐ Additional Information and Analyses Sections: 9	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.		☒ Yes ☐ No
Signature/date/time stamp: Swapan K. De -S Digitally signed by Swapan K. De -S Date: 2024.07.25 09:25:56 -04'00'					

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory	Consent To Include on Public List of Reviewers
Pharmacology/Toxicology Team Leader	Donald Charles Thompson OND/ONDP/NPDPTS	☐ Benefit-Risk Assessment ☐ Interdisciplinary Assessment ☐ Additional Information and Analyses Sections 7.1	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.		☒ Yes ☐ No
Signature/date/time stamp: D Charles Thompson -S Digitally signed by D Charles Thompson -S Date: 2024.07.26 11:59:08 -04'00'					

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory	Consent To Include on Public List of Reviewers
Pharmacology/Toxicology Reviewer	Chibueze Ihunnah OND/ONDP/NPDPTS	☐ Benefit-Risk Assessment ☐ Interdisciplinary Assessment ☐ Additional Information and Analyses Sections: 7.1	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.		☒ Yes ☐ No
Signature/date/time stamp: Chibueze Ihunnah -S Digitally signed by Chibueze Ihunnah -S Date: 2024.07.26 11:53:48 -04'00'					

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory	Consent To Include on Public List of Reviewers
Controlled Substance Staff Reviewer	Chad Reissig OCD/CSS	☐ Benefit-Risk Assessment ☐ Interdisciplinary Assessment ☐ Additional Information and Analyses Sections: 7.7.3	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	CSS reviewed this application from an abuse potential perspective. The application assessment of "No deficiencies preclude approval" applies *only* to abuse potential.	☒ Yes ☐ No
Signature/date/time stamp: Chad Reissig -S Digitally signed by Chad Reissig -S Date: 2024.07.25 11:14:30 -04'00'					
Clinical Pharmacology Team Leader	Yuching Yang OTS/OCP/DPM	☐ Benefit-Risk Assessment ☐ Interdisciplinary Assessment ☒ Additional Information and Analyses Sections: 5, 6.3, 14.5	Based on my assessment of the application: ☐ No deficiencies preclude approval. ☒ Deficiencies preclude approval. ☐ Not applicable.		☒ Yes ☐ No
Signature/date/time stamp: Manuela Grimstein signing on behalf of Yuching Yang Manuela D. Grimstein -S Digitally signed by Manuela D. Grimstein -S Date: 2024.07.25 14:50:41 -04'00'					

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory	Consent To Include on Public List of Reviewers
Clinical Pharmacology Reviewer	Manuela Grimstein OTS/OCP/DPM	☐ Benefit-Risk Assessment ☐ Interdisciplinary Assessment ☒ Additional Information and Analyses Sections: 5, 6.3, 14.5	Based on my assessment of the application: ☐ No deficiencies preclude approval. ☒ Deficiencies preclude approval. ☐ Not applicable.		☒ Yes ☐ No
Signature/date/time stamp: Manuela D. Grimstein -S Digitally signed by Manuela D. Grimstein -S Date: 2024.07.25 14:50:04 -04'00'					
Clinical Signatory Authority	Nushin Todd OND/ONPD/DNPDI	☒ Benefit-Risk Assessment ☒ Interdisciplinary Assessment ☒ Additional Information and Analyses Sections:	Based on my assessment of the application: ☐ No deficiencies preclude approval. ☒ Deficiencies preclude approval. ☐ Not applicable.		☒ Yes ☐ No
Signature/date/time stamp: Nushin Todd -S Digitally signed by Nushin Todd -S Date: 2024.07.26 14:26:01 -04'00'					

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/

TAM M DINH
07/26/2024 06:00:37 PM

DOROTHY N CHANG
07/26/2024 06:01:51 PM

NUSHIN F TODD
07/26/2024 06:12:14 PM