

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**217338Orig1s000**

**MULTI-DISCIPLINE REVIEW**

**Summary Review**

**Clinical Review**

**Non-Clinical Review**

**Statistical Review**

**Clinical Pharmacology Review**

**NDA/BLA Multi-Disciplinary Review and Evaluation**

|                                                       |                                                                                                                                                                                                                                    |
|-------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Application Type</b>                               | NDA Class 2 Resubmission                                                                                                                                                                                                           |
| <b>Application Number(s)</b>                          | 217338                                                                                                                                                                                                                             |
| <b>Priority or Standard</b>                           | Standard                                                                                                                                                                                                                           |
| <b>Submit Date(s)</b>                                 | July 7, 2025                                                                                                                                                                                                                       |
| <b>Received Date(s)</b>                               | July 7, 2025                                                                                                                                                                                                                       |
| <b>PDUFA Goal Date</b>                                | January 7, 2026                                                                                                                                                                                                                    |
| <b>Division/Office</b>                                | Division of Nonprescription Drugs I (DNPDI)                                                                                                                                                                                        |
| <b>Review Completion Date</b>                         | January 7, 2026                                                                                                                                                                                                                    |
| <b>Established/Proper Name</b>                        | Guaifenesin, dextromethorphan hydrobromide and naproxen Sodium                                                                                                                                                                     |
| <b>(Proposed) Trade Name</b>                          | Mucinex 12HR Cold & Fever Multi-Symptom                                                                                                                                                                                            |
| <b>Pharmacologic Class</b>                            | Expectorant, antitussive, analgesic/antipyretic                                                                                                                                                                                    |
| <b>Applicant</b>                                      | RB Health (US) LLC                                                                                                                                                                                                                 |
| <b>Dosage form</b>                                    | Extended-release tablets                                                                                                                                                                                                           |
| <b>Dosing Strength</b>                                | Each tablet contains 600 mg guaifenesin, 30 mg dextromethorphan hydrobromide, and 110 mg naproxen sodium                                                                                                                           |
| <b>Applicant proposed Dosing Regimen</b>              | <ul style="list-style-type: none"> <li>• Adults and children 12 years and older: Take 2 tablets every 12 hours. Not to exceed 4 tablets per 24 hours.</li> <li>• Children under 12 years of age: Do not use.</li> </ul>            |
| <b>Applicant Proposed Indication(s)/Population(s)</b> | <ul style="list-style-type: none"> <li>• Helps loosen phlegm (mucus) and thin bronchial secretions to rid the bronchial passageways of bothersome mucus and make coughs more productive</li> <li>• Temporarily relieves</li> </ul> |

|                                                                                             |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|---------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                                                             | <ul style="list-style-type: none"> <li>○ Cough due to minor throat and bronchial irritation as may occur with the common cold or inhaled irritants</li> <li>○ The intensity of coughing</li> <li>○ The impulse to cough to help you get to sleep</li> <li>○ Minor aches and pains due to headache and the common cold</li> <li>• Temporarily reduces fever</li> </ul>                                                                                                                                                                                                                                                                                                      |
| <b>Applicant Proposed SNOMED CT Indication Disease Term for each Proposed Indication</b>    | 22253000 Pain (finding), 386661006 Fever (finding), 417850002 Respiratory tract congestion and cough (disorder), 82272006 Common Cold (disorder)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| <b>Recommendation on Regulatory Action</b>                                                  | Approval                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| <b>Recommended Indication(s)/Population(s)</b><br>(if applicable)                           | <p>For adults and children 12 years and older:</p> <ul style="list-style-type: none"> <li>• Helps loosen phlegm (mucus) and thin bronchial secretions to rid the bronchial passageways of bothersome mucus and make coughs more productive</li> <li>• Temporarily relieves               <ul style="list-style-type: none"> <li>○ Cough due to minor throat and bronchial irritation as may occur with the common cold or inhaled irritants</li> <li>○ The intensity of coughing</li> <li>○ The impulse to cough to help you get to sleep</li> <li>○ Minor aches and pains due to headache and the common cold</li> </ul> </li> <li>• Temporarily reduces fever</li> </ul> |
| <b>Recommended SNOMED CT Indication Disease Term for each Indication</b><br>(if applicable) | 22253000 Pain (finding), 386661006 Fever (finding), 417850002 Respiratory tract congestion and cough (disorder), 82272006 Common Cold (disorder)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| <b>Recommended Dosing Regimen</b>                                                           | <ul style="list-style-type: none"> <li>• Adults and children 12 years and older: Take 2 tablets every 12 hours. Not to exceed 4 tablets per 24 hours.</li> <li>• Children under 12 years of age: Do not use.</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                    |

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{guaifenesin/dextromethorphan hydrobromide/naproxen sodium tablets}

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## Reviewers of Multi-Disciplinary Review and Evaluation

|                                                            |                   |
|------------------------------------------------------------|-------------------|
| <b>Regulatory Project Manager</b>                          | Tam Dinh          |
| <b>Nonclinical Reviewer</b>                                | Chibueze Ihunnah  |
| <b>Nonclinical Team Leader</b>                             | Jennifer White    |
| <b>Office of Clinical Pharmacology Reviewer(s)</b>         | Sanjida Mahjabeen |
| <b>Office of Clinical Pharmacology Second reviewer</b>     | Yunzhao Ren       |
| <b>DNPD 1 Clinical Reviewer</b>                            | Aklil Getachew    |
| <b>DNPD 1 Clinical Team Leader</b>                         | Shila Azodi       |
| <b>Labeling Reviewer</b>                                   | Michelle Walker   |
| <b>Labeling Team Leader</b>                                | Robert Bahde      |
| <b>Cross-Disciplinary Team Leader</b>                      | Yunzhao Ren       |
| <b>Office Director (or designated signatory authority)</b> | Nushin Todd       |

## Additional Reviewers of Application

|                  |                               |
|------------------|-------------------------------|
| <b>OPQ</b>       | Swapn De, Danae Christodoulou |
| <b>OSE/DMEPA</b> | Grace Jones, Tingting Gao     |
| <b>Other</b>     |                               |

OPQ=Office of Pharmaceutical Quality

OPDP=Office of Prescription Drug Promotion

OSI=Office of Scientific Investigations

OSE=Office of Surveillance and Epidemiology

DEPI=Division of Epidemiology

DMEPA=Division of Medication Error Prevention and Analysis

DRISK=Division of Risk Management

**Signatures**

| DISCIPLINE                                                                                                                          | REVIEWER        | OFFICE/DIVISION | SECTIONS AUTHORED/<br>APPROVED | AUTHORED/<br>APPROVED                                                                                   |
|-------------------------------------------------------------------------------------------------------------------------------------|-----------------|-----------------|--------------------------------|---------------------------------------------------------------------------------------------------------|
| Regulatory<br>Project<br>Management<br><br>Regulatory<br>Project Manager                                                            | Tam Dinh        | OND/ORO/DRO-NPD | Section: 3                     | <b>Select one:</b><br><input checked="" type="checkbox"/> Authored<br><input type="checkbox"/> Approved |
| <b>Signature:</b> TAM DINH -S<br><small>Digitally signed by TAM DINH -S<br/>Date: 2025.12.22 10:32:23 -05'00'</small>               |                 |                 |                                |                                                                                                         |
| Regulatory<br>Project<br>Management<br><br>CPMS                                                                                     | Daniel Brum     | OND/ORO/DRO-NPD | Section: 3                     | <b>Select one:</b><br><input type="checkbox"/> Authored<br><input checked="" type="checkbox"/> Approved |
| <b>Signature:</b> DANIEL BRUM -S<br><small>Digitally signed by DANIEL BRUM -S<br/>Date: 2025.12.22 11:27:54 -05'00'</small>         |                 |                 |                                |                                                                                                         |
| Interdisciplinary<br>Scientist<br><br>Team Leader                                                                                   | Robert Bahde    | OND/ONPD/DNPDI  | Section: 10                    | <b>Select one:</b><br><input type="checkbox"/> Authored<br><input checked="" type="checkbox"/> Approved |
| <b>Signature:</b> Robert J. Bahde -S<br><small>Digitally signed by Robert J. Bahde -S<br/>Date: 2025.12.22 11:22:13 -05'00'</small> |                 |                 |                                |                                                                                                         |
| Interdisciplinary<br>Scientist<br><br>Reviewer                                                                                      | Michelle Walker | OND/ONPD/DNPDI  | Section: 10                    | <b>Select one:</b><br><input checked="" type="checkbox"/> Authored<br><input type="checkbox"/> Approved |
| <b>Signature:</b> Michelle Walker -S<br><small>Digitally signed by Michelle Walker -S<br/>Date: 2025.12.22 10:40:56 -05'00'</small> |                 |                 |                                |                                                                                                         |

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| Nonclinical<br>Reviewer              | Chibueze<br>Ihunnah                                                                                                      | OND/ONDP/NPDPTS | Sections: 5                       | <b>Select one:</b><br><input checked="" type="checkbox"/> Authored<br><input type="checkbox"/> Approved |
|                                      | <b>Signature:</b> CHIBUEZE IHUNNAH -S Digitally signed by CHIBUEZE IHUNNAH -S<br>Date: 2025.12.22 11:57:36 -05'00'       |                 |                                   |                                                                                                         |
| Nonclinical<br>Team Leader           | Jennifer White                                                                                                           | OND/ONDP/NPDPTS | Sections: 5                       | <b>Select one:</b><br><input type="checkbox"/> Authored<br><input checked="" type="checkbox"/> Approved |
|                                      | <b>Signature:</b> Jennifer J. White -S Digitally signed by Jennifer J.<br>White -S<br>Date: 2025.12.22 12:25:57 -05'00'  |                 |                                   |                                                                                                         |
| Clinical<br>Pharmacology<br>Reviewer | Sanjida<br>Mahjabeen                                                                                                     | OTS/OCP/DIIP    | Sections: 1, 6, 14.4,             | <b>Select one:</b><br><input checked="" type="checkbox"/> Authored<br><input type="checkbox"/> Approved |
|                                      | <b>Signature:</b> Sanjida Mahjabeen -S Digitally signed by Sanjida Mahjabeen -<br>S<br>Date: 2025.12.22 12:20:51 -05'00' |                 |                                   |                                                                                                         |

| DISCIPLINE                                  | REVIEWER                                                                                                       | OFFICE/DIVISION | SECTIONS<br>AUTHORED/<br>APPROVED | AUTHORED/<br>APPROVED                                                                                   |
|---------------------------------------------|----------------------------------------------------------------------------------------------------------------|-----------------|-----------------------------------|---------------------------------------------------------------------------------------------------------|
| Clinical Pharmacology<br>Secondary Reviewer | Yunzhao Ren                                                                                                    | OTS/OCP/DIIP    | Section: 1, 6, 14.4               | <b>Select one:</b><br><input type="checkbox"/> Authored<br><input checked="" type="checkbox"/> Approved |
|                                             | <b>Signature:</b> Yunzhao Ren -S Digitally signed by Yunzhao Ren -S<br>Date: 2025.12.22 12:14:46 -05'00'       |                 |                                   |                                                                                                         |
| Clinical Reviewer                           | Aklil Getachew                                                                                                 | OND/ONPD/DNPDI  | Sections: 7.1, 7.3, 7.4, 9        | <b>Select one:</b><br><input checked="" type="checkbox"/> Authored<br><input type="checkbox"/> Approved |
|                                             | <b>Signature:</b> AKLIL GETACHEW -S Digitally signed by AKLIL GETACHEW -S<br>Date: 2025.12.22 12:10:13 -05'00' |                 |                                   |                                                                                                         |

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|------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------|-----------------------------------|---------------------------------------------------------------------------------------------------------|
| Clinical Team<br>Leader                                                                              | Shila Azodi                                                                                                                                              | OND/ONPD/DNPD1  | Sections: 7.1, 7.3, 7.4, 9        | <b>Select one:</b><br><input type="checkbox"/> Authored<br><input checked="" type="checkbox"/> Approved |
|                                                                                                      | Nushin Todd signing on behalf on Shila Azodi<br><b>Signature:</b> Nushin Todd -S Digitally signed by Nushin Todd -S<br>Date: 2025.12.22 13:47:21 -05'00' |                 |                                   |                                                                                                         |
| Product Quality<br>Senior<br>Pharmaceutical<br>Quality<br>Assessor,<br>Application<br>Team<br>Leader | Swapn De                                                                                                                                                 | OPQOPQAI/IX     | Sections: 4.1                     | <b>Select one:</b><br><input type="checkbox"/> Authored<br><input checked="" type="checkbox"/> Approved |
|                                                                                                      | <b>Signature:</b> SWAPAN K. DE -S Digitally signed by SWAPAN K.<br>DE -S<br>Date: 2025.12.22 13:05:50 -05'00'                                            |                 |                                   |                                                                                                         |
| Cross-<br>Disciplinary<br>Team Leader                                                                | Yunzhao Ren                                                                                                                                              | OTS/OCP/DIIP    | Sections:1-12, 14                 | <b>Select one:</b><br><input type="checkbox"/> Authored<br><input checked="" type="checkbox"/> Approved |
|                                                                                                      | <b>Signature:</b> Yunzhao Ren -S Digitally signed by Yunzhao Ren -S<br>Date: 2025.12.22 12:15:12 -05'00'                                                 |                 |                                   |                                                                                                         |
| Division Director<br>(Clinical)                                                                      | Nushin Todd                                                                                                                                              | OND/ONPD/DNPD1  | Sections: All                     | <b>Select one:</b><br><input type="checkbox"/> Authored<br><input checked="" type="checkbox"/> Approved |
|                                                                                                      | <b>Signature:</b> Nushin Todd -S Digitally signed by Nushin Todd -S<br>Date: 2025.12.22 13:50:35 -05'00'                                                 |                 |                                   |                                                                                                         |

## Glossary

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|      |                                         |
|------|-----------------------------------------|
| AE   | adverse event                           |
| CFR  | Code of Federal Regulations             |
| CMC  | chemistry, manufacturing, and controls  |
| CRL  | Complete Response Letter                |
| CSS  | Controlled Substance Staff              |
| ECG  | electrocardiogram                       |
| ER   | extended-release                        |
| FDA  | Food and Drug Administration            |
| FDC  | fixed dose combination                  |
| IR   | integrated review                       |
| NDA  | new drug application                    |
| OPQ  | Office of Pharmaceutical Quality        |
| OSE  | Office of Surveillance and Epidemiology |
| PDP  | principal display panel                 |
| PI   | prescribing information                 |
| PK   | pharmacokinetics                        |
| PMC  | postmarketing commitment                |
| PMR  | postmarketing requirement               |
| PREA | Pediatric Research Equity Act           |
| PRO  | patient reported outcome                |
| REMS | risk evaluation and mitigation strategy |
| SAE  | serious adverse event                   |
| SOC  | standard of care                        |
| SOI  | statement of identity                   |
| TEAE | treatment emergent adverse event        |

## 1 Executive Summary

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### 1.1. Product Introduction

RB Health (US) LLC resubmitted NDA 217338 on July 7, 2025, seeking marketing approval of for Mucinex 12HR Cold & Fever Multi-Symptom (guaifenesin 600 mg, dextromethorphan hydrobromide 30 mg, and naproxen sodium 110 mg) extended-release (ER) tablets for nonprescription use. It is the first drug product with a combination of these three active pharmaceutical ingredients. 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 dosing instruction for this fixed dose combination (FDC) ER formulation in adults and children 12 years of age and older is to take two tablets every 12 hours.

The proposed product is a bilayer tablet comprising an immediate-release portion (b) (4) and an extended-release layer (b) (4).

This 505(b)(2) application relies on FDA's previous findings of safety and effectiveness for NDA 021620 (Mucinex DM), NDA 020204 (Aleve), and NDA 021076 (Aleve-D Sinus and Cold).

### 1.2. Conclusions on the Substantial Evidence of Effectiveness

The recommended regulatory action for this resubmission is Approval.

The Applicant has demonstrated substantial evidence of effectiveness through establishing appropriate scientific bridges between the proposed product and the listed drugs via the 505(b)(2) pathway. The scientific bridges consist of two relative bioavailability studies (Study RB5-US-1505 and Study 0225104).

In the original submission dated September 29, 2023, Study RB5-US-1505 cross-referenced their own Mucinex DM (NDA 021620) by demonstrating the bioequivalence of the guaifenesin

and dextromethorphan components between the proposed product and Mucinex DM under fasted condition with the 90% confidence intervals of geometric mean ratios of  $C_{\max}$  and AUCs within the acceptance range of 80.00-125.00%. The study also demonstrated that there is no clinically relevant food effect on the guaifenesin component of the proposed product; and the food effect on the dextromethorphan is similar between the proposed product and Mucinex DM.

In addition, the same study demonstrated the bioequivalence of the naproxen component between the proposed product and the listed drug (Aleve, NDA 020204) under fasted condition with the 90% confidence intervals of geometric mean ratios of  $C_{\max}$  and AUCs within the acceptance range of 80.00-125.00%. The study also demonstrated that there is no clinically relevant food effect on the naproxen component of the proposed product.

A Complete Response Letter (CRL) was issued on July 26, 2024, primarily based on a potential efficacy concern of the naproxen component of the proposed drug product, as the proposed dosing interval is every 12 hours whereas the approved dosing interval for the listed drug (Aleve, NDA 020204) is every 8 to 12 hours.

To address the efficacy concern, the Applicant conducted another relative bioavailability Study 0225104 and resubmitted the NDA on July 7, 2025. A different naproxen-containing listed drug (Aleve-D Sinus and Cold, NDA 021076) with an approved dosing interval of every 12 hours was used in Study 0225104. Study 0225104 demonstrated the bioequivalence of the naproxen component between the proposed product and the listed drug (Aleve-D Sinus and Cold, NDA 021076) under fasted condition with the 90% confidence intervals of geometric mean ratios of  $C_{\max}$  and AUCs within the acceptance range of 80.00-125.00%.

The appropriately established bioequivalence-based scientific bridges allow the Applicant to cross-reference guaifenesin and dextromethorphan to their own product Mucinex; and rely on FDA's finding of safety and effectiveness for the listed drugs for naproxen, including the approved dose, dosing regimen, and relevant indications.

### 1.3. Benefit-Risk Assessment

| Dimension                           | Evidence and Uncertainties                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | Conclusions and Reasons                                                                                                                                                                                                                                                                                                                         |
|-------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b><u>Analysis of Condition</u></b> | <ul style="list-style-type: none"> <li>The common cold is one of the most frequently occurring illnesses that affect millions of Americans annually (Heikkinen and Järvinen 2003<sup>1</sup>).</li> <li>Colds can be caused by more than 200 different respiratory viruses (Eccles 2023<sup>2</sup>).</li> <li>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<sup>3</sup>).</li> <li>Symptoms of the common cold may include cough, mucus production, minor aches and pains, headache, and fever among other symptomatology.</li> <li>Though they are self-limited and generally not considered a serious medical condition, colds can be bothersome to consumers and affect quality of life.</li> </ul> | <ul style="list-style-type: none"> <li>The common cold affects millions of Americans annually.</li> <li>Symptoms caused by the common cold can be uncomfortable and can temporarily affect quality of life.</li> <li>Symptoms associated with the common cold are generally self-diagnoseable and self-manageable for lay consumers.</li> </ul> |

<sup>1</sup> Heikkinen, T and A Järvinen, 2003, The common cold, Lancet, 361(9351):51-59

<sup>2</sup> Eccles, R, 2023, Common cold, Front Allergy, 4:1224988

<sup>3</sup> Eccles, R, 2023, Common cold, Front Allergy, 4:1224988

NDA/BLA Multi-disciplinary Review and Evaluation {NDA 217338}  
{guaifenesin/dextromethorphan hydrobromide/naproxen sodium tablets}

| Dimension                               | Evidence and Uncertainties                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | Conclusions and Reasons                                                                                                                                                                                                                                                                                     |
|-----------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                         | <ul style="list-style-type: none"> <li>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<sup>4</sup>).</li> </ul>                                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                             |
| <b><u>Current Treatment Options</u></b> | <ul style="list-style-type: none"> <li>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.</li> <li>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<sup>5</sup> and those approved under section 505(b) of the Federal Food, Drug, and Cosmetic Act.</li> </ul> | <ul style="list-style-type: none"> <li>Consumers rely on available safe and effective nonprescription drugs for symptomatic relief of symptoms associated with the common cold.</li> <li>A variety of treatment options are currently available for multi-symptom management of the common cold.</li> </ul> |

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<sup>4</sup> Fendrick, AM, AS Monto, B Nightengale, and M Sarnes, 2003, The economic burden of non-influenza-related viral respiratory tract infection in the United States, Arch Intern Med, 163(4):487-494

<sup>5</sup> Final Administrative Order (OTC000026) Over-the-Counter Monograph M012: Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products for Over-the-Counter Human Use; October 14, 2022; [https://www.accessdata.fda.gov/drugsatfda\\_docs/omuf/Order/OTC%20Monograph\\_M012-Cough%20Cold%20Allergy%20Bronchodilator%20and%20Antiasthmatic%20Drug%20Products%20for%20OTC%20Human%20Use%2010.14.2022\\_0.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/omuf/Order/OTC%20Monograph_M012-Cough%20Cold%20Allergy%20Bronchodilator%20and%20Antiasthmatic%20Drug%20Products%20for%20OTC%20Human%20Use%2010.14.2022_0.pdf)

NDA/BLA Multi-disciplinary Review and Evaluation {NDA 217338}  
{guaifenesin/dextromethorphan hydrobromide/naproxen sodium tablets}

| Dimension                              | Evidence and Uncertainties                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | Conclusions and Reasons                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
|----------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b><u>Benefit</u></b>                  | <ul style="list-style-type: none"> <li>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.</li> <li>In two relative bioavailability studies, the proposed FDC product demonstrated BE of each of its three active pharmaceutical ingredients with those of the approved Mucinex DM (guaifenesin/dextromethorphan HBr, a product owned by the same Applicant, NDA 021620) and the listed drug Aleve-D Sinus and Cold (naproxen sodium, NDA 021076), under fasted condition.</li> <li>The proposed FDC product's dosing instruction of every 12 hours is identical to the dosing interval for Mucinex DM and Aleve-D Sinus and Cold.</li> </ul> | <ul style="list-style-type: none"> <li>The proposed FDC product would present consumers with another alternative for nonprescription management of symptoms caused by the common cold.</li> <li>The Applicant has provided sufficient data to support its proposed dose and dosing interval based on the listed drugs.</li> </ul>                                                                                                                                                                            |
| <b><u>Risk and Risk Management</u></b> | <ul style="list-style-type: none"> <li>Single ingredient products containing guaifenesin, dextromethorphan HBr, and naproxen sodium have been marketed as nonprescription drugs for decades.</li> <li>The safety profile for each active pharmaceutical ingredient is well characterized.</li> <li>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.</li> <li>In the postmarketing safety data evaluating cases reporting concomitant use of all three active ingredients, there were</li> </ul>                                    | <ul style="list-style-type: none"> <li>There were no SAEs or significant safety findings from the clinical program for this FDC product.</li> <li>There were no significant findings in the postmarketing safety data when looking at concomitant use of all three active ingredients.</li> <li>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</li> </ul> |

NDA/BLA Multi-disciplinary Review and Evaluation {NDA 217338}  
{guaifenesin/dextromethorphan hydrobromide/naproxen sodium tablets}

| Dimension | Evidence and Uncertainties                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | Conclusions and Reasons               |
|-----------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------|
|           | <p>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.</p> <ul style="list-style-type: none"><li>• 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.</li></ul> | <p>relative to existing products.</p> |

## 1.4. Patient Experience Data

**Patient Experience Data Relevant to this Application** (check all that apply)

|                          |                                                                                                                                    |                                                  |
|--------------------------|------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------|
| <input type="checkbox"/> | <b>The patient experience data that were submitted as part of the application include:</b>                                         | Section of review where discussed, if applicable |
| <input type="checkbox"/> | Clinical outcome assessment (COA) data, such as                                                                                    |                                                  |
| <input type="checkbox"/> | Patient reported outcome (PRO)                                                                                                     |                                                  |
| <input type="checkbox"/> | Observer reported outcome (ObsRO)                                                                                                  |                                                  |
| <input type="checkbox"/> | Clinician reported outcome (ClinRO)                                                                                                |                                                  |
| <input type="checkbox"/> | Performance outcome (PerfO)                                                                                                        |                                                  |
| <input type="checkbox"/> | Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.) |                                                  |
| <input type="checkbox"/> | Patient-focused drug development or other stakeholder meeting summary reports                                                      |                                                  |
| <input type="checkbox"/> | Observational survey studies designed to capture patient experience data                                                           |                                                  |
| <input type="checkbox"/> | Natural history studies                                                                                                            |                                                  |
| <input type="checkbox"/> | Patient preference studies (e.g., submitted studies or scientific publications)                                                    |                                                  |
| <input type="checkbox"/> | Other: (Please specify):                                                                                                           |                                                  |
| <input type="checkbox"/> | <b>Patient experience data that were not submitted in the application, but were considered in this review:</b>                     |                                                  |
| <input type="checkbox"/> | Input informed from participation in meetings with patient stakeholders                                                            |                                                  |

|                                     |                                                                               |  |
|-------------------------------------|-------------------------------------------------------------------------------|--|
| <input type="checkbox"/>            | Patient-focused drug development or other stakeholder meeting summary reports |  |
| <input type="checkbox"/>            | Observational survey studies designed to capture patient experience data      |  |
| <input type="checkbox"/>            | Other: (Please specify):                                                      |  |
| <input checked="" type="checkbox"/> | <b>Patient experience data was not submitted as part of this application.</b> |  |

## 2 Therapeutic Context

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### 2.1. 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<sup>6</sup>; Arroll 2011<sup>7</sup>). 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<sup>8</sup>). The National Institute of Allergy and Infectious Disease estimated that individuals in the United States suffer more than 1 billion colds annually (Wein 2009<sup>9</sup>). 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<sup>10</sup>).

### 2.2. 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 1](#) (NDA approved products) and [Table 2](#) (monograph drug products). Due to the large

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<sup>6</sup> Heikkinen, T and A Järvinen, 2003, The common cold, Lancet, 361(9351):51-59

<sup>7</sup> Arroll, B, 2011, Common cold, BMJ Clin Evid, 2011

<sup>8</sup> Heikkinen, T and A Järvinen, 2003, The common cold, Lancet, 361(9351):51-59

<sup>9</sup> Wein, H, 2009, Understanding a Common Cold Virus, NIH Research Matters, (April 13)

<sup>10</sup> Fendrick, AM, AS Monto, B Nightengale, and M Sarnes, 2003, The economic burden of non-influenza-related viral respiratory tract infection in the United States, Arch Intern Med, 163(4):487-494

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 1. 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   | <ul style="list-style-type: none"> <li>Ibuprofen 200 mg</li> <li>Pseudoephedrine HCl 30 mg</li> </ul>        | <ul style="list-style-type: none"> <li>Pain reliever/fever reducer</li> <li>Nasal decongestant</li> </ul> | Oral capsule:<br>1 capsule every 4 – 6 hours |
| Advil Cold and Sinus   | <ul style="list-style-type: none"> <li>Ibuprofen 200 mg</li> <li>Pseudoephedrine HCl 30 mg</li> </ul>        | <ul style="list-style-type: none"> <li>Pain reliever/fever reducer</li> <li>Nasal decongestant</li> </ul> | Oral caplet:<br>1 caplet every 4 – 6 hours   |
| Aleve-D Sinus and Cold | <ul style="list-style-type: none"> <li>Naproxen sodium 220 mg</li> <li>Pseudoephedrine HCl 120 mg</li> </ul> | <ul style="list-style-type: none"> <li>Pain reliever/fever reducer</li> <li>Nasal decongestant</li> </ul> | Oral caplet:<br>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 2. 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<br>Cough suppressant                  | Tablet, capsule, solution |
| Acetaminophen, Chlorpheniramine maleate                   | Pain reliever/fever reducer<br>Antihistamine                      | Tablet, capsule           |
| Acetaminophen, Guaifenesin                                | Pain reliever/fever reducer<br>Expectorant                        | Capsule, solution         |
| Acetaminophen, Dextromethorphan HBr, Guaifenesin          | Pain reliever/fever reducer<br>Cough suppressant<br>Expectorant   | Capsule, solution         |
| Acetaminophen, Dextromethorphan HBr, Doxylamine succinate | Pain reliever/fever reducer<br>Cough suppressant<br>Antihistamine | Tablet, capsule, solution |

NDA/BLA Multi-disciplinary Review and Evaluation {NDA 217338}

{guaifenesin/dextromethorphan hydrobromide/naproxen sodium tablets}

| Active Ingredients                                                         | Purpose                                                                                 | Dosage Form(s)   |
|----------------------------------------------------------------------------|-----------------------------------------------------------------------------------------|------------------|
| Acetaminophen, Dextromethorphan HBr, Chlorpheniramine maleate              | Pain relief/ fever reducer<br>Cough suppressant<br>Antihistamine                        | Tablet, solution |
| Acetaminophen, Dextromethorphan HBr, Diphenhydramine                       | Pain relief/ fever reducer<br>Cough suppressant<br>Antihistamine                        | Solution         |
| Acetaminophen, Dextromethorphan HBr, Pseudoephedrine HCl                   | Pain reliever/fever reducer<br>Cough suppressant<br>Nasal decongestant                  | Tablet           |
| Acetaminophen, Dextromethorphan HBr, Chlorpheniramine, Pseudoephedrine HCl | Pain reliever/fever reducer<br>Cough suppressant<br>Antihistamine<br>Nasal decongestant | Tablet           |
| Acetaminophen, Dextromethorphan HBr, Guaifenesin, Pseudoephedrine HCl      | Pain reliever/fever reducer<br>Cough suppressant<br>Expectorant<br>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

### 3 Regulatory Background

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#### 3.1. U.S. Regulatory Actions and Marketing History

The proposed combination product contains three active pharmaceutical ingredients: naproxen sodium 110 mg, dextromethorphan HBr 30 mg, and guaifenesin 600 mg. There is no such triple-combination product currently marketed in the United States.

The individual active pharmaceutical ingredients have established U.S. marketing histories. Specifically, the listed drug or cross-reference drug for this application have been widely marketed in the United States as stated below:

- Mucinex DM (guaifenesin 600 mg/dextromethorphan HBr 30 mg extended-release tablets, NDA 021620) was owned by the same Applicant and originally approved on April 29, 2004, and has been marketed in the United States since that date.
- Aleve (naproxen sodium 220 mg tablets, NDA 020204) was originally approved on January 11, 1994, and has been marketed in the United States since that date.
- Aleve-D Sinus and Cold (naproxen sodium 220 mg/pseudoephedrine HCl 120 mg extended-release tablets, NDA 021076) was originally approved on November 29, 1999, and was marketed in the United States; however, this product is currently discontinued. The current Orange Book reference standard for this product is naproxen sodium and pseudoephedrine HCl extended-release tablets (ANDA 076518, Application holder: Perrigo), which was approved on March 17, 2004.

#### 3.2. Summary of Presubmission/Submission Regulatory Activity

##### **September 29, 2023**

NDA 217338 was submitted, seeking marketing approval for the fixed-dose combination extended-release drug product Mucinex 12HR Cold & Fever Multi-Symptom (each tablet contains naproxen sodium 110 mg, dextromethorphan hydrobromide 30 mg, and guaifenesin 600 mg) for nonprescription use. The proposed dosing regimen is two tablets every 12 hours for adults and children 12 years and older. This 505(b)(2) application relies on FDA's previous findings of safety and effectiveness for NDA 021620 (Mucinex DM), NDA 020204 (Aleve), and NDA 021076 (Aleve-D Sinus and Cold).

### **July 26, 2024**

FDA issued a CRL (Reference ID 5420432)<sup>11</sup> with following primary deficiency:

*You have not provided sufficient evidence to support the proposed 12-hour duration of action and dosing regimen for your proposed ER product. The submitted pharmacokinetic (PK) data demonstrate that each component of the proposed fixed dose combination product is bioequivalent (BE) with that from approved listed drugs, Mucinex DM (guaifenesin 600 mg; dextromethorphan hydrobromide 30 mg ER tablet [NDA 021620]) and Aleve (naproxen sodium tablet [NDA 020204]). However, Aleve has a dosing direction that instructs consumers to take 1 tablet (i.e., 220 mg naproxen sodium) every 8 to 12 hours while symptoms last and allows consumers to take 2 tablets within the first hour for the first dose. Demonstration of BE of the naproxen component from your drug to Aleve is not adequate to support the modification of the dosing interval to the proposed 12-hour dosing interval.*

In addition, the CRL listed two potential approaches to address this deficiency:

1. *Provide clinical efficacy data to support a 12-hour duration of use when studied in a relevant patient population, or*
2. *Conduct a relative bioavailability study to establish a scientific bridge between the proposed product and Aleve-D Sinus and Cold (naproxen sodium 220 mg; pseudoephedrine HCl 120 mg extended-release tablet [NDA 021076]).*

### **September 26, 2024**

A Type A meeting request and briefing package was submitted. FDA provided preliminary meeting comments on October 28, 2024 (Reference ID 5469432), which disagreed with PBPK approach; meanwhile generally agreed with the primary endpoints (i.e.,  $C_{max}$ ,  $AUC_{0-t}$ , and  $AUC_{0-inf}$ ) and the listed drug (i.e., ANDA 076518) of the proposed Study 0225104.

### **July 7, 2025**

NDA 217338 was resubmitted to address the deficiencies outlined in the July 26, 2024 CRL. The resubmission included the clinical study report for Study 0225104 and supporting analyses demonstrating bioequivalence between the naproxen sodium component of the proposed product and Aleve-D Sinus and Cold.

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<sup>11</sup> FDA Complete Response Letter, NDA 217338, July 26, 2024, DARRTS Reference ID 5420432

## **4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety**

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### **4.1. Product Quality**

Regarding quality aspects of the application, the drug substance, drug product, biopharmaceutics, process, and facility sections were reviewed during the previous review cycle and found adequate to support approval of the application. The drug product has been granted a shelf life of 36 months in all container closure configurations.

In brief, no new CMC information is included in the resubmission of this NDA. The manufacturing facilities remain in acceptable status and the product quality information for this application remain adequate to support the NDA.

## 5 Nonclinical Pharmacology/Toxicology

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### 5.1. Executive Summary

No new or original nonclinical data were requested or submitted to support safety of the active ingredients or excipients in the proposed drug product. During the previous review cycle, the Pharmacology/Toxicology reviewer conducted a safety assessment of the proposed excipients in the proposed formulation. At that time, it was determined that the proposed excipients were supported by their use in the approved drug products with similar clinical conditions of use and/or by a supportive food additive regulation published in the Code of Federal Regulations (CFR). Furthermore, there are no proposed changes to the proposed formulation provided in the current resubmission compared to the original submission. For additional details, refer to the nonclinical pharmacology/toxicology review and safety assessment provided during the original review cycle.

## 6 Clinical Pharmacology

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### 6.1. Executive Summary

RB Health (US) LLC resubmitted NDA 217338 on July 7, 2025, seeking to address the dosing regimen-related clinical efficacy concern listed in the CRL dated July 26, 2024 (refer to Section [3.2](#)).

In this submission (July 7, 2025), the Applicant included the study report from a newly conducted relative bioavailability study (Study 0225104). Study 0225104 is a phase 1, open-label, single-dose, randomized, 2-way crossover relative bioavailability study comparing the naproxen component of the proposed product to the listed drug Aleve-D Sinus and Cold (NDA 021076) under fasted condition. The study established bioequivalence between the naproxen component of the proposed product and the listed drug, Aleve-D Sinus and Cold, providing the necessary scientific bridge to support the proposed every 12-hour dosing regimen.

The clinical pharmacology program for this NDA consists of data from Studies RB5-US-1505 and 0225104, provides adequate scientific justification for the proposed every 12-hour dosing regimen for all three active pharmaceutical ingredients of the proposed FDC product. Study RB5-US-1505 established bioequivalence of guaifenesin and dextromethorphan between the proposed product and the cross-reference product Mucinex DM, while Study 0225104 specifically addressed the dosing interval concern by demonstrating bioequivalence to a naproxen-containing product (Aleve-D Sinus and Cold) that is approved for dosing every 12 hours. The data included in the current resubmission resolves the naproxen dosing regimen-related concern listed in the CRL dated July 26, 2024.

**Recommendation:** The Office of Clinical Pharmacology, Division of Inflammation and Immune Pharmacology (DIIP), recommends **approval** of this application from a clinical pharmacology perspective. The submitted data adequately support the proposed every 12-hour dosing regimen and establish appropriate scientific bridges to the cross-referenced or listed drugs.

### 6.2. Summary of Clinical Pharmacology Assessment

The clinical pharmacology assessment for this resubmission included review of pharmacokinetic data from a relative bioavailability study 0225104, as well as associated bioanalytical methods. The resubmission assessment focused on establishing bioequivalence with naproxen listed drug and specifically addressing the 12-hour dosing interval for the proposed FDC product. The current review focuses on Study 0225104, which established the scientific basis for the every 12-hour regimen of the naproxen component. For detailed assessment of Study RB5-US-1505 to establish the scientific bridge between the other two active ingredients (i.e., guaifenesin and dextromethorphan) and Mucinex DM, refer to the original NDA 217338 Integrated Review

dated July 26, 2024.

### **6.2.1. Pharmacology and Clinical Pharmacokinetics**

#### **Naproxen**

Naproxen is a nonsteroidal anti-inflammatory drug with analgesic and antipyretic properties. The mean  $AUC_{0-inf}$  and  $C_{max}$  of naproxen following a single dose of the proposed product (220 mg naproxen sodium, 60 mg dextromethorphan HBr, and 1200 mg guaifenesin) under fasted condition is  $604 \pm 118 \mu\text{g}\cdot\text{h/mL}$  and  $39 \pm 10 \mu\text{g/mL}$ , respectively (Study 0225104). The median  $T_{max}$  is 1.5 hours. High fat meal does not have a clinically relevant effect on AUC and  $C_{max}$  of naproxen (Study RB5-US-1505).

According to drug label of NDA 018164, naproxen has a volume of distribution of 0.16 L/kg. At therapeutic levels naproxen is greater than 99% albumin-bound. Naproxen is extensively metabolized to 6-O-desmethyl naproxen, and both parent and metabolites do not induce metabolizing enzymes. Approximately 95% of the naproxen from any dose is excreted in the urine, primarily as naproxen (less than 1%), 6-O-desmethyl naproxen (less than 1%) or their conjugates (66% to 92%).

#### **Dextromethorphan**

Dextromethorphan is an uncompetitive antagonist of the N-methyl-D-aspartate (NMDA) receptor and a sigma-1 receptor agonist. The mean  $AUC_{0-inf}$  and  $C_{max}$  of dextromethorphan following a single dose of the proposed product (220 mg naproxen sodium, 60 mg dextromethorphan HBr, and 1200 mg guaifenesin) under fasted condition is  $272 \pm 657 \text{ ng}\cdot\text{h/mL}$  and  $302 \pm 695 \mu\text{g/mL}$ , respectively (Study RB5-US-1505). The median  $T_{max}$  is 6 hours. High fat meal does increase  $AUC_{0-inf}$  and  $C_{max}$  of dextromethorphan by 34% and 24%, respectively. The magnitude of increase in exposure is similar between the proposed drug product and the Mucinex DM.

According to drug label of NDA 215430, dextromethorphan is primarily metabolized by CYP2D6 to dextrorphan. In CYP2D6 extensive metabolizers, approximately 37-52% of the orally administered dose of dextromethorphan is recovered in the urine. Less than 2% of the administered dose is excreted as unchanged parent drug in the urine. In CYP2D6 poor metabolizers, approximately 45-83% of the administered dose is recovered in the urine.

Approximately 26% of the administered dose is excreted as unchanged parent drug in the urine.

#### **Guaifenesin**

Guaifenesin is an expectorant, the action of which promotes or facilitates the removal of secretions from the respiratory tract. The mean  $AUC_{0-inf}$  and  $C_{max}$  of naproxen following a single

dose of the proposed product (220 mg naproxen sodium, 60 mg dextromethorphan HBr, and 1200 mg guaifenesin) under fasted condition is  $8059 \pm 3240 \mu\text{g}\cdot\text{h/mL}$  and  $1871 \pm 793 \mu\text{g/mL}$ , respectively (Study 0225104). The median  $T_{\text{max}}$  is 1 hour. High fat meal does not have a clinically relevant effect on AUC and  $C_{\text{max}}$  of guaifenesin (Study RB5-US-1505).

### **6.2.2. General Dosing and Therapeutic Individualization**

#### **General Dosing**

The proposed dosing regimen is 220 mg naproxen sodium, 60 mg dextromethorphan HBr, and 1200 mg guaifenesin (i.e., two tablets with the dosing strength of each tablet as 110 mg naproxen sodium, 30 mg dextromethorphan HBr, and 600 mg guaifenesin) every 12 hours in adults and children 12 years of age and older.

#### **Therapeutic Individualization**

No specific dose adjustments are proposed. The product follows the same age restrictions as the listed drugs (to be used in adults and children 12 years and older).

#### **Outstanding Issues**

None.

## **6.3.Comprehensive Clinical Pharmacology Review**

### **6.3.1. General Pharmacology and Pharmacokinetic Characteristics**

Throughout the review, the proposed drug product has been designated as (b) (4) tablets which was the initial proprietary name used by the Applicant in the product development studies prior to submission of the current NDA.

Study 0225104 was a phase 1, open-label, single-dose, randomized, 2-way crossover relative bioavailability study conducted to establish a scientific bridge between the proposed product and Aleve-D Sinus and Cold. Twenty-six healthy participants were randomized and dosed (19 male, 7 female; mean age 31.3 years) with a 5-day washout period. Participants received either two (b) (4) tablets (total 220 mg naproxen sodium, 60 mg dextromethorphan HBr, and 1200 mg guaifenesin) or one Aleve-D Sinus and Cold tablet (220 mg naproxen sodium and 120 mg pseudoephedrine) under fasted conditions, using the current Orange Book reference standard (ANDA 076518) as agreed upon by the FDA. Refer to Section [14.4.1](#) for detail review on Study design and analysis plan.

The PK profiles and statistical summary of naproxen systemic exposures from two treatment groups observed in Study 0225104 are provided in [Figure 1](#) and [Table 3](#), respectively. The study

demonstrated similar PK profiles between the proposed product and Aleve-D Sinus and Cold under fasted conditions for the naproxen component ([Figure 1](#)). The median  $T_{max}$  of naproxen was delayed by 0.75 hours for the proposed product compared to Aleve-D Sinus and Cold. The clinical meaning of the slight difference between two median  $T_{max}$  values is unclear, as both of them are within the historically reported ranges. For example, in the Biopharmaceutics review of Aleve-D Sinus and Cold<sup>12</sup>, Study S97-050 conducted under fasted condition demonstrated that, naproxen  $T_{max}$  was  $1.26 \pm 0.95$  hours for Aleve-D Sinus and Cold and  $1.13 \pm 0.92$  hours for the reference product, Aleve. Similarly, the Clinical Pharmacology review of Aleve PM showed that in Study 16135, under fasted conditions, naproxen  $T_{max}$  was 1.25 hours (range: 0.33-3.0 hours) for the combination product<sup>13</sup>.

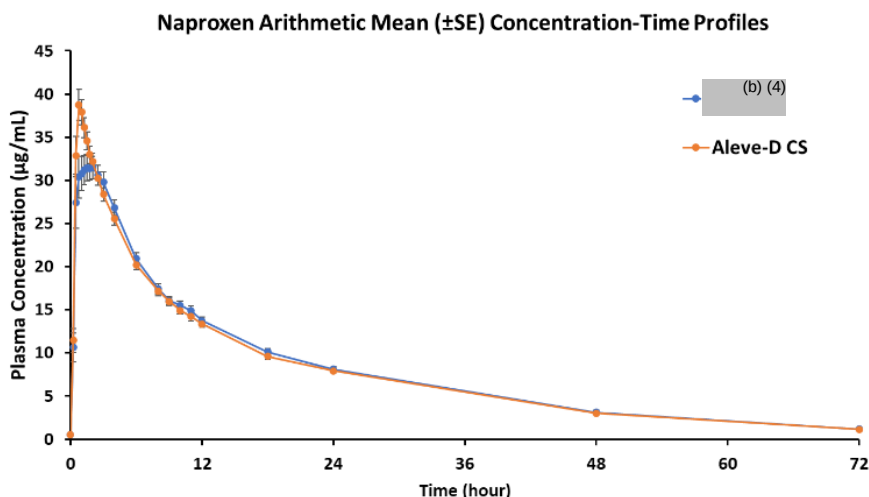
The mean elimination half-life was similar between treatments (17.63 hours for (b) (4) vs. 17.84 hours for Aleve-D Sinus and Cold). These PK findings are consistent with the naproxen PK results from Study RB5-US-1505 included in the original NDA submission, which demonstrated comparable elimination half-life (~18-20 hours) and bioequivalence with Aleve.

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<sup>12</sup> The FDA's biopharmaceutics review of Aleve-D Sinus and Cold (NDA 21-076); [https://www.accessdata.fda.gov/drugsatfda\\_docs/nda/99/21-076\\_Aleve\\_biopharmr.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/nda/99/21-076_Aleve_biopharmr.pdf)

<sup>13</sup> The FDA's clinical pharmacology review of Aleve PM (NDA 205352) [https://www.accessdata.fda.gov/drugsatfda\\_docs/nda/2014/205352Orig1s000ClinPharmR.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/205352Orig1s000ClinPharmR.pdf)

**Figure 1. Observed Arithmetic Mean PK Profiles of Naproxen Following 220 mg Single Dose in Study 0225104**



Source: FDA Analysis using ADPC.xpt from Study 0225104. All the post-dose BLQ concentrations were imputed with 1/2 value of LLOQ (0.5 µg/mL).  
Abbreviations: Aleve-D CS; Aleve-D Sinus & Cold, mg, milligram; min, minute; mL, milliliter; µg, microgram; PK, pharmacokinetic; SE, standard error

**Table 3. Statistical Summary of PK Parameters of Naproxen Obtained From Study 0225104**

| Parameter <sup>1</sup>                      | Treatment A<br>(N=26)<br>( (b) (4) tablets) | Treatment B<br>(N=26)<br>(Aleve-D Sinus and Cold tablet) |
|---------------------------------------------|---------------------------------------------|----------------------------------------------------------|
| AUC <sub>0-inf</sub> (µg·h/mL)              | 604.36 ± 117.85                             | 595.14 ± 109.86                                          |
| AUC <sub>0-72h</sub> (µg·h/mL)              | 572.55 ± 99.83                              | 563.13 ± 88.11                                           |
| C <sub>max</sub> (µg/mL)                    | 39.01 ± 9.73                                | 41.47 ± 7.09                                             |
| Elimination half-life, t <sub>1/2</sub> (h) | 16.94 ± 3.08                                | 17.12 ± 3.74                                             |
| T <sub>max</sub> (h) <sup>2</sup>           | 1.5 (0.5 - 4.0)                             | 0.75 (0.5 - 2.5)                                         |

Source: FDA Analysis using ADPC.xpt from Study 0225104. All the post-dose BLQ concentrations were imputed with 1/2 value of LLOQ (0.5 µg/mL).

<sup>1</sup> All values are expressed in Arithmetic mean ± SD

<sup>2</sup> Median (min, max)

Abbreviations: AUC<sub>0-inf</sub>, area under the concentration-time curve estimated to infinity; AUC<sub>0-72h</sub>, area under the concentration-time curve from time 0 to 72 hours; C<sub>max</sub>, maximum plasma concentration; h, hour; mL, milliliter; N, number (of population); µg - microgram; SD, standard deviation; T<sub>max</sub>, time to maximum concentration; t<sub>1/2</sub>, half-life

Study 0225104 showed that all primary PK parameters met bioequivalence criteria, with 90% CIs for geometric mean ratios of  $C_{max}$  (87.07-98.25%),  $AUC_{0-72h}$  (99.31-103.56%), and  $AUC_{0-inf}$  (98.8-104.01%) within the acceptance range of 80.00-125.00% as shown in [Table 4](#).

**Table 4. Statistical Comparisons of PK Parameters of Naproxen Under Fasted Conditions from Study 0225104**

| Parameter                      | Listed Drug<br>(Aleve-D Sinus<br>& Cold)<br>GeoLSM | Proposed Product<br>( <span style="background-color: #cccccc;">(b) (4)</span> )<br>GeoLSM | T/R Ratio [90% CI]      |
|--------------------------------|----------------------------------------------------|-------------------------------------------------------------------------------------------|-------------------------|
| $C_{max}$ (µg/mL) (n=26)       | 40.89                                              | 37.82                                                                                     | 92.49% (87.07-98.25%)   |
| $AUC_{0-72h}$ (µg*h/mL) (n=26) | 556.98                                             | 564.87                                                                                    | 101.41% (99.31-103.56%) |
| $AUC_{0-inf}$ (µg*h/mL) (n=26) | 586.38                                             | 594.43                                                                                    | 101.37% (98.8-104.01%)  |

Source: FDA Analysis using ADPC.xpt from Study 0225104. All the post-dose BLQ concentrations were imputed with 1/2 value of LLOQ

(0.5 µg/mL).

Abbreviations:  $AUC_{0-inf}$ , area under the concentration-time curve estimated to infinity;  $AUC_{0-72h}$ , area under the concentration-time curve from time 0 to 72 hours; CI, confidence interval;  $C_{max}$ , maximum plasma concentration; GeoLSM, geometric least squares mean; h, hour; mL, milliliter; N, number (of population); T/R, test/reference ratio; µg - microgram

Study 0225104 therefore established bioequivalence between the naproxen component of the proposed product and Aleve-D Sinus and Cold, providing the necessary scientific bridge to support the every 12-hour dosing regimen and addressing the deficiency identified in the CRL dated July 26, 2024. The bioanalytical methods were reasonably validated and the Office of Clinical Pharmacology has no outstanding concerns regarding this application.

### 6.3.2. Clinical Pharmacology Questions

#### Does the clinical pharmacology program provide supportive evidence of effectiveness?

Yes, the clinical pharmacology program provides supportive evidence of effectiveness through establishment of appropriate scientific bridges to the cross-reference drug and the listed drugs for all three active pharmaceutical ingredients. The proposed dosing regimen of two tablets every 12 hours is supported by the same approved dosing regimen of the listed drug products.

The scientific bridges are established by demonstration of bioequivalence between the proposed product and the cross-reference drug and the listed drugs through two key studies. Study RB5-US-1505 demonstrated bioequivalence of all three active pharmaceutical ingredients to Mucinex DM and Aleve under fasted conditions, with 90% confidence intervals of geometric mean ratios of  $C_{max}$  and AUCs within the acceptance range of 80.00-125.00%. Study 0225104 specifically addressed every 12-hour dosing interval concern by establishing bioequivalence

between the naproxen component and Aleve-D Sinus and Cold, which is approved with every 12-hour dosing interval. The overall clinical program in this resubmission provides the necessary scientific bridge to allow the Applicant to rely on FDA's finding of safety and effectiveness for the listed drugs.

**Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?**

Yes, the proposed dosing regimen of 220 mg naproxen sodium, 60 mg dextromethorphan HBr, and 1200 mg guaifenesin every 12 hours in adults and children 12 years of age and older is appropriate for the general patient population, as the same dosing regimen is approved for the listed drugs.

**Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?**

Refer to the drug facts of the cross-reference drug product [Mucinex DM (NDA 021620) and the listed drug product Aleve-D Sinus and Cold (NDA 021076)], no alternative dosing regimens are needed for subpopulations based on intrinsic factors.

The Applicant did not seek approval of drug product in children under 12 years of age, as naproxen is not approved for nonprescription use in this population. Per the agreed initial pediatric study plan (dated June 1, 2019), the FDA granted clinical study waivers for subjects aged 0-17 years, allowing extrapolation of adult PK data to support use in the 12-17 age group.

**Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?**

No clinically relevant food-drug interactions were identified. Study RB5-US-1505 demonstrated no significant food effect on systemic exposure of guaifenesin and naproxen components, with 90% CIs of geometric mean ratios for  $C_{max}$  and AUCs between fasted and fed conditions within 80-125%. Dextromethorphan showed increased exposure with food (34% increase in  $C_{max}$ ); however, this effect was similar to the cross-reference drug product Mucinex DM and supports administration regardless of food. The proposed labeling recommends taking with food or milk if stomach upset occurs, consistent with the labeling for Aleve-D Sinus and Cold and Aleve.

No dedicated drug-drug interaction studies were conducted under this NDA. The proposed labeling incorporates established drug interaction warnings from the listed drugs. Key interactions include contraindication with monoamine oxidase inhibitors for dextromethorphan and potential serotonin syndrome with concomitant serotonergic drugs. The naproxen component includes standard NSAID warnings regarding interactions with anticoagulants and potential interference with aspirin's cardioprotective effects. The Applicant conducted an in

vitro dose dumping study and concluded that alcohol does not significantly impact dissolution of the three ingredients compared to the listed drugs<sup>14</sup>.

**Were the bioanalytical methods supporting the two pivotal studies for this application adequate?**

Yes, the bioanalytical methods supporting both pivotal studies were adequate. Both methods were conducted at qualified laboratories and met regulatory standards for bioequivalence studies. *Refer to Section 14.4.2 in this review for detail assessment.*

For Study RB5-US-1505, a validated LC-MS/MS bioanalytical method simultaneously determined concentrations of all three analytes in human plasma with appropriate lower limits of quantification (0.01 ng/mL for dextromethorphan, 5 ng/mL for guaifenesin, and 50 ng/mL for naproxen). The method demonstrated acceptable precision (CV ≤6.8%), accuracy (relative error within ±4.8% to 6.7%), and satisfactory in-study performance with passing rates >94% for all analytes and incurred sample reanalysis meeting acceptance criteria. *Refer to the original NDA 217338 Integrated Review, Section 14 for detail assessment.*

For Study 0225104, a validated HPLC-MS/MS method was used for naproxen determination with a lower limit of quantification of 1.00 µg/mL. The bioanalytical laboratory ( (b) (4) ) conducted the analysis using established validated methods, with all samples analyzed within the established storage period.

## 7 Sources of Clinical Data and Review Strategy

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### 7.1. Table of Clinical Studies

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NDA/BLA Multi-disciplinary Review and Evaluation {NDA 217338}  
{guaifenesin/dextromethorphan hydrobromide/naproxen sodium tablets}

**Table 5. Listing of Clinical Studies Relevant to this NDA**

| Study Identifier                       | Objective of Study                | Study Design and Type of Control                                                                                                                                                                       | Test Product (s)                                                                                                                                                                                                                                                    | Treatment Duration | No. of patients enrolled | Study Population |
|----------------------------------------|-----------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------|--------------------------|------------------|
| <b><i>Pivotal Clinical Studies</i></b> |                                   |                                                                                                                                                                                                        |                                                                                                                                                                                                                                                                     |                    |                          |                  |
| RB5-US-1505                            | Relative BA vs. reference product | Open label, randomized, balanced, 4-treatment, 4-period, crossover BA study of an experimental combination ER test product vs. co-administration of reference products under fasted and fed conditions | <u>Test product:</u><br>ER guaifenesin 600 mg/dextromethorphan HBr 30mg/naproxen 220 mg bilayer tablet<br><br><u>Reference product:</u><br>Co-administration of Mucinex DM (guaifenesin 600 mg/dextromethorphan HBr 30mg) tablet and naproxen sodium (220mg) tablet | Single dose        | 102                      | Healthy Subjects |
| 0225104                                | Relative BA vs. reference product | Open label, randomized, 2-way crossover relative BA study to analyze the naproxen sodium IR plasma concentrations from 2 x ER test product vs. reference product under fasting conditions              | <u>Test product:</u><br>ER guaifenesin 600 mg/dextromethorphan HBr 30mg/naproxen 220 mg bilayer tablet<br>( (b) (4) )<br><br><u>Reference product:</u><br>Naproxen sodium 220 mg IR and pseudoephedrine hydrochloride 120 mg ER (Aleve-D Sinus and Cold)            | Single dose        | 26                       | Healthy Subjects |

NDA/BLA Multi-disciplinary Review and Evaluation {NDA 217338}  
{guaifenesin/dextromethorphan hydrobromide/naproxen sodium tablets}

| <b><i>Pilot Clinical Studies</i></b> |                                            |                                                                                                                                                                                                                                                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |             |    |                     |
|--------------------------------------|--------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------|----|---------------------|
| 2009-<br>GGE-TRI-<br>DM              | Relative BA<br>vs.<br>reference<br>product | Open label, randomized, balanced,<br>4-treatment, 4-period, crossover BA<br>study of 2 experimental<br>combination ER test product under<br>fasted and fed condition vs co-<br>administration of reference<br>products under fasted conditions | <p><u>Treatment A:</u></p> <p>(b) (4) formulation ER guaifenesin 600<br/>mg/ dextromethorphan HBr<br/>30mg/naproxen 220 mg bilayer<br/>tablet under fasting condition</p> <p><u>Treatment B:</u></p> <p>(b) (4) formulation ER guaifenesin<br/>600 mg/ dextromethorphan HBr<br/>30mg/naproxen 220 mg bilayer<br/>tablet under fasting condition</p> <p><u>Treatment C:</u></p> <p>(b) (4) formulation ER guaifenesin 600<br/>mg/ dextromethorphan HBr<br/>30mg/naproxen 220 mg bilayer<br/>tablet under fed condition</p> <p><u>Reference product:</u></p> <p>Co-administration of Mucinex<br/>(guaifenesin) 600mg, Vicks Formula<br/>44 Custom Care 30 mg syrup, and<br/>Aleve (naproxen sodium 220mg)</p> | Single dose | 30 | Healthy<br>Subjects |

NDA/BLA Multi-disciplinary Review and Evaluation {NDA 217338}  
{guaifenesin/dextromethorphan hydrobromide/naproxen sodium tablets}

|                   |                                   |                                                                                                                                                                                                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |             |    |                  |
|-------------------|-----------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------|----|------------------|
| 2014-MUCDM-NAP-02 | Relative BA vs. reference product | Open label, randomized, balanced, 5-treatment, 5-period, crossover BA study of 2 experimental combination ER test products vs. co- administration of reference products under fasted and fed conditions | <p><u>Treatment A:</u></p> <p>2 (b) (4) of (b) (4) formulation ER guaifenesin 600 mg/ dextromethorphan HBr 30mg/naproxen 110 mg bilayer tablet under fasting condition</p> <p><u>Treatment B:</u></p> <p>2 (b) (4) of (b) (4) formulation ER guaifenesin 600 mg/ dextromethorphan HBr 30mg/naproxen 110 mg bilayer tablet under fed condition</p> <p><u>Treatment C:</u></p> <p>2 (b) (4) of (b) (4) formulation ER guaifenesin 600 mg/ dextromethorphan HBr 30mg/naproxen 110 mg bilayer tablet under fasting condition</p> <p><u>Treatment D:</u></p> <p>2 (b) (4) of (b) (4) formulation ER guaifenesin 600 mg/ dextromethorphan HBr</p> | Single dose | 25 | Healthy Subjects |
|-------------------|-----------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------|----|------------------|

NDA/BLA Multi-disciplinary Review and Evaluation {NDA 217338}  
{guaifenesin/dextromethorphan hydrobromide/naproxen sodium tablets}

|  |  |  |                                                                                                                                                                                                                                                              |  |  |  |
|--|--|--|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--|--|--|
|  |  |  | <p>30mg/naproxen 110 mg bilayer tablet under fed condition</p> <p><u>Reference product:</u></p> <p>Co-administration of 2 Mucinex DM (guaifenesin 600 mg/dextromethorphan HBr 30mg) tablets and 1 naproxen sodium (220mg) tablet under fasting condition</p> |  |  |  |
|--|--|--|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--|--|--|

## **7.2.Review of Safety**

### **7.2.1. Safety Review Approach**

This safety review centers on clinical safety data from PK study 0225104. For the comprehensive safety assessment of this drug product, refer to the Integrated Review (IR) dated July 26, 2024 (DAARTS Reference ID: 5420429).

The safety review for this proposed fixed-dose combination (FDC) product establishes that while each of the three active ingredients has well-established individual safety profiles from longstanding nonprescription use, the main focus is determining whether the combination can be safely used without a healthcare intermediary.

The Applicant supported combination safety through PK study data with pivotal PK study RB5-US-1505 demonstrating bioequivalence (Section 7.6 of IR) and through two exploratory PK studies (Section 17 of IR) that were conducted with earlier formulations of the FDC product (Pilot studies 2009-GGE-TRI-DM and 2014-MUCDM-NAP-02). Additionally, comprehensive postmarketing safety evaluations (Section 7.6.2 of IR) were completed using multiple databases (internal pharmacovigilance, FAERS, WHO Vigibase, NPDS) and literature reviews (Section 7.6.2.2 of IR) to identify any unexpected or serious adverse events associated with concomitant use of guaifenesin, dextromethorphan, and naproxen. Furthermore, given dextromethorphan's known abuse potential, the Controlled Substance Staff (CSS) was consulted to evaluate abuse and misuse risks for the proposed product, with their full review completed on January 22, 2024 (Section 7.7.3 of IR).

### **7.2.2. Review of the Safety Database**

#### **Overall Exposure**

A total of 183 subjects were randomized across all four PK studies and received at least one dose of the study drug. 102 subjects were enrolled in Study RB5-US-1505, 26 subjects were enrolled in Study 0225104, 30 subjects were enrolled in Study 2009-GGE-TRI-DM and 25 subjects were enrolled in Study 2014-MUCDM-02.

#### **Adequacy of the Safety Database:**

Study RB5-US-1505 and Study 0225104 both used the intend-to-market formulation. Given the well-established safety profiles of each active ingredient and extensive postmarketing experience, the safety database generated from the PK studies is adequate.

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 was reviewed in the Integrated Review. These evaluations were conducted

according to expectations for a nonprescription application and were considered adequate to support the review.

### 7.2.3. Adequacy of Applicant's Clinical Safety Assessments

#### Issues Regarding Data Integrity and Submission Quality

None.

#### Categorization of Adverse Events

FDA defines an adverse event (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 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 6](#).

**Table 6. 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 7](#).

**Table 7. 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

## 7.2.4. Safety Results

### Overview and Objectives

#### **Study 0225104**

The primary objective of this study was:

To assess the relative BA in rate and extent of exposure of active ingredient IR naproxen sodium from Treatment A (two (b) (4) tablets) relative to that from Treatment B (one Aleve-D Sinus and Cold tablet) in healthy adults in the fasted state.

The secondary objectives of this study were to:

- Assess other pharmacokinetic (PK) parameters for naproxen sodium related to rBA between Treatment A (b) (4) and Treatment B (Aleve-D Sinus and Cold)
- Assess the safety and tolerability of test product and reference product in healthy adults

### Methodology

The study consisted of a pre-study screening visit followed by two treatment periods, a washout period and an end of study visit conducted at Day 5 (+2 days) after the last dose. Each of the treatment periods were 5 days in duration. The total duration of study participation was 6 weeks.

Subjects who met the inclusion and exclusion criteria were assessed for final eligibility and admitted to the Clinical Unit for an overnight fast. Subjects were randomized to receive the treatment sequence AB or BA on Day of Treatment Period 1. Randomized participants received either Treatment A (b) (4) or Treatment B (Aleve-D Sinus and Cold).

The treatments for each period included:

- A: Two (b) (4) bi-layer ER tablets each containing 600 mg guaifenesin, 30 mg dextromethorphan hydrobromide, and 110 mg naproxen sodium, administered with 240 mL of water after an overnight fast of 10-hours

- B: One Aleve-D Sinus and Cold ER Tablet containing 220 mg naproxen sodium and 120 mg pseudoephedrine hydrochloride, administered with 240 mL of water after an overnight fast of 10 hours

During the study, blood samples were collected at various time points to measure the concentration of naproxen in the participants' plasma. There was washout of 5 days between the last dose of Treatment Period 1 and first dose of Treatment Period 2 to allow complete elimination of the study drug before subsequent dosing, based on 5 elimination half-lives of naproxen.

Adverse events (AEs), medical history, vital signs, physical exam (PE), electrocardiogram (ECG), routine laboratory tests (hematology, biochemistry, urinalysis, urine for drugs of abuse, and urine pregnancy [if applicable]) were measured as safety endpoints.

### **Demographics**

The study population consisted of 19 male subjects (19/26; 73.1%) and 7 female subjects (7/26; 26.9%). Most subjects were White (20/26; 76.9%); the rest were Black or African American (6/26; 23.1%). All (100%) of subjects were Hispanic or Latino. Subjects' ages ranged from 21-41 years with a mean age of 31.3. The mean BMI (SD) was 25.35 kg/m<sup>2</sup>.

### **Deaths**

There were no deaths.

### **Serious Adverse Events**

There were no serious adverse events.

### **Dropouts and/or Discontinuations Due to Adverse Effects**

There were no dropouts and/or discontinuations from the study.

### **Significant Adverse Events**

There were no significant adverse events.

### **Treatment Emergent Adverse Events and Adverse Reactions**

Twenty-six subjects were randomized, received a dose of the study drug, and completed the treatment period. Two participants (2/26; 7.7%) did not return for the follow up visit and did not complete the study and were considered lost to follow up per the study protocol. Twenty-four (24/26; 92.3%) of participants completed the study. All 26 randomized participants who received a dose of the study drug were included in the safety population.

Seven participants (7/26; 26.9%) reported a total of fifteen Treatment Emergent Adverse Events (TEAEs). Four participants (4/26; 15.4%) reported seven TEAEs after receiving Treatment A ( (b) (4) ) and five participants (5/26; 19.2%) reported eight TEAEs after receiving Treatment B (Aleve-D Sinus and Cold). Thirteen of the total TEAEs (13/15; 86.7%) were considered mild in severity. Two TEAEs (2/15; 13.3%) reported in one participant after receiving Treatment B (Aleve-D Sinus and Cold) were moderate in severity ([Table 8](#)).

**Table 8. TEAEs and Severity by Treatment Group**

|                                         | Total (N=26) | Treatment A<br>(b) (4)<br>(N=26) | Treatment B<br>Aleve-D Sinus and<br>Cold<br>(N=26) |
|-----------------------------------------|--------------|----------------------------------|----------------------------------------------------|
| <b>Number of subjects reporting AEs</b> | 7 (26.9%)    | 4 (15.4%)                        | 5 (19.2%)                                          |
| <b>TEAEs</b>                            | 15           | 7                                | 8                                                  |
| <b>Severity</b>                         |              |                                  |                                                    |
| <b>Mild</b>                             | 13           | 7                                | 6                                                  |
| <b>Moderate</b>                         | 2            | 0                                | 2                                                  |
| <b>Severe</b>                           | 0            | 0                                | 0                                                  |

Source: Table generated by reviewer. Adapted from data in eCTD, Module 5.3.1.1 Study 0225104.

Abbreviations: AE, adverse event; N, number (of population); (b) (4) TEAE, treatment-emergent adverse event

Among the 15 TEAEs, the most frequent System Organ Class (SOC) was Investigations with 8 out of 15 (8/15; 53.3 %) of TEAEs. The second most affected SOC was Musculoskeletal and Connective Tissue Disorders with two TEAEs (2/15; 13.3%) in this category. Other SOC with single occurrences were in the Cardiac Disorder, Infections and Infestations, Nervous system disorders, Injury, poisoning, and procedural complications and Skin and subcutaneous tissue disorder ([Table 9](#)).

There were 3 TEAEs out of 15 that were not resolved by the end of the study and 2 that needed intervention.

**Table 9. Reported TEAEs by Treatment Group, Severity, Resolution and Need for Intervention**

| SOC /PTs                                                     | Total<br>(N=26)  | Treat<br>ment<br>A<br>(N=26) | Treatment<br>B<br>(N=26) | Severity | Resolved<br>by EOS | Need for<br>interventio<br>n |
|--------------------------------------------------------------|------------------|------------------------------|--------------------------|----------|--------------------|------------------------------|
| <b>Investigations</b>                                        | <b>8 (53.3%)</b> |                              |                          |          |                    |                              |
| ALT increased                                                |                  |                              | 1                        | Mild     | yes                | no                           |
| CPK                                                          |                  | 1                            |                          | Mild     | yes                | no                           |
| Eosinophil increase                                          |                  |                              | 2                        | Mild     | No (1 of 2)        | no                           |
| Heart rate increased                                         |                  | 1                            |                          | Mild     | yes                | no                           |
| Nitrite urine<br>increased                                   |                  | 1                            |                          | Mild     | No                 | no                           |
| WBC increased                                                |                  |                              | 1                        | Mild     | yes                | no                           |
| WBC in urine positive                                        |                  | 1                            |                          | Mild     | No                 | no                           |
| <b>Musculoskeletal &amp;<br/>connective tissue disorders</b> | <b>2 (13.3%)</b> |                              |                          |          |                    |                              |
| Pain in extremity                                            |                  | 1                            | 1                        | Moderate | yes                | yes                          |
| <b>Cardiac Disorders</b>                                     | <b>1 (6.7%)</b>  |                              |                          |          |                    |                              |
| Palpitations                                                 |                  |                              | 1                        | Mild     | yes                | no                           |
| <b>Infections and Infestations</b>                           | <b>1 (6.7%)</b>  |                              |                          |          |                    |                              |
| Cellulitis                                                   |                  |                              | 1                        | Moderate | yes                | yes                          |
| <b>Injury, poisoning and<br/>procedural complications</b>    | <b>1 (6.7%)</b>  |                              |                          |          |                    |                              |
| Skin abrasion                                                |                  | 1                            |                          | Mild     | yes                | no                           |
| <b>Nervous system disorder</b>                               | <b>1 (6.7%)</b>  |                              |                          |          |                    |                              |

|                                               |                 |   |   |      |     |     |
|-----------------------------------------------|-----------------|---|---|------|-----|-----|
| Presyncope                                    |                 |   | 1 | Mild | yes | no  |
| <b>Skin and subcutaneous tissue disorders</b> | <b>1 (6.7%)</b> |   |   |      |     |     |
| Pruritus                                      |                 | 1 |   | Mild | yes | Yes |

Source: Table generated by reviewer.

Adapted from data in eCTD, Module 5.3.1.1 Study 0225104.

Abbreviations: SOC, System Organ Class; PT, Preferred Terms; N, number (of population); ALT, alanine transaminase; CPK, creatinine phosphokinase; WBC, white blood cell count, EOS, end of study

### **Analyses of TEAEs by Treatment Group** ([Table 9](#))

#### **Treatment A ( (b) (4) )**

Four participants (4/26;15.4%) reported seven TEAEs after receiving Treatment A ( (b) (4) ). All TEAEs were considered mild in intensity. All TEAEs except for two TEAEs in one participant were resolved by the end of the study. One TEAE needed intervention.

TEAEs that were unresolved and/or needed treatment

1. Participant (b) (6) was found to have nitrite and white blood cells in the urinalysis. No treatment was given for this event. The event was ongoing at the end of the study (not recovered/ not resolved). These two TEAEs were considered to be mild in intensity and unrelated to the treatment.
2. Participant (b) (6) had pruritus that was treated with Aquaphor and resolved without further intervention. The TEAE was considered to be mild in intensity and was thought to be unrelated to the treatment.

#### **Treatment B (Aleve-D Sinus and Cold)**

Five participants reported eight TEAEs after receiving Treatment B (Aleve-D Sinus and Cold). Six of the eight TEAEs were considered mild in intensity, two TEAEs reported in one participant were moderate in intensity and required treatment and one TEAE in the Treatment B group was not resolved by the end of the study.

TEAEs that were unresolved and/or needed treatment

1. Participant (b) (6) had leg pain that was eventually diagnosed as cellulitis of the left leg. The participant received saline gauze, oral antibiotics (cephalexin) and acetaminophen. The events were considered to be moderate in intensity. The events were resolved by the end of the study and were not considered to be related to the treatment.
2. Participant (b) (6) had progressively increased ALT levels reaching a peak on Day 5 (received Treatment A on Day 1). The subject had marginally elevated levels before receiving study drug (Pre dose level) which was considered to be clinically insignificant by the personal investigator (PI). The increased ALT level resolved by the end of the

study. The TEAE was considered to be mild in intensity and did resolve without intervention.

3. Participant (b) (6) had increased eosinophilic, and leukocyte count after receiving Treatment A. This elevated count remained increased by the end of the study period (unresolved). This TEAE was considered mild in intensity and thought to be related to an allergic reaction per the PI and unrelated to the treatment. No treatment was given for the event.

*Reviewer's comment:*

*All TEAEs except for two were mild in severity. The two TEAEs considered moderate in severity were due to pain and cellulitis of the leg unrelated to the study drug. Almost all TEAEs were considered unrelated to study drug. The one TEAE thought to be possibly related to Treatment A had an elevated ALT level that possibly had an onset preceding the study drug.*

**Laboratory Findings**

Laboratory evaluations (performed pre and post study) included complete blood count with differential; serum chemistry (sodium, potassium, chloride, urea, creatinine) total protein, albumin, total bilirubin, alkaline phosphatase, ALT, AST, creatinine kinase, fasting glucose, total cholesterol, triglycerides, HDL/ LDL cholesterol and urinalysis. Also tested were antibodies to HIV, hepatitis B and hepatitis C and urine screen for drugs of abuse (opiates cannabis amphetamines), alcohol breath test and pregnancy test (urine and serum).

**Laboratory Abnormalities:**

5 subjects had at least one abnormal laboratory result ([Table 10](#))

- Subject (b) (6) had increased leukocyte and neutrophil count. These elevated counts were closely related to possible cellulitis of the leg. Both increased counts resolved by the end of the visit.
- Subject (b) (6) had increased eosinophil and eosinophil/leukocyte counts. These events were considered to be related to an allergic reaction. The increased counts were not resolved by EOS.
- Subject (b) (6) had an increased creatinine kinase level. Levels normalized without treatment at the EOS visit.
- Subject (b) (6) had increased ALT levels that normalized without treatment by the EOS visit.
- Subject (b) (6) had a positive nitrite and white blood cells in the urine. The events were ongoing and unresolved by the EOS.

**Table 10. Subjects With Abnormal Laboratory Values by Treatment Groups**

| Preferred Term                                    | Treatment A | Treatment B |
|---------------------------------------------------|-------------|-------------|
| WBC count Increased                               |             | 1           |
| Eosinophil count Increased                        |             | 1           |
| Blood creatinine kinase increased                 | 1           |             |
| Alanine aminotransferase Increased                |             | 1           |
| Nitrite urine and White blood cells urine present | 1           |             |

Source: Table generated by reviewer.  
Adapted from data in eCTD, Module 5.3.1.1 Study 0225104.  
Abbreviations: WBC, white blood cell count

*Reviewer Comment: Laboratory testing did not reveal any specific or clinically significant safety findings.*

### **Vital Signs**

Vital signs including blood pressure, heart rate, respiratory rate and temperature were collected at baseline and end of study.

One participant (Participant (b) (6)) had an elevated heart rate 4 days after administration of Treatment A and 1 day prior to receiving Treatment B. The increased heart rate remained elevated until the end of the study. The elevated level was not considered clinically significant. No treatment was given for this AE and the event resolved by the end of the study.

*Reviewer Comment: On review of this participant's vital signs, the heart rate was elevated on Treatment Day 5 (112 beats/minute), 4 days after receiving Treatment A, then peaked at 122 beats/minute, 5 days post dose Treatment A, pre dose Treatment B on Day 6. The heart rate remained elevated at the follow up visit at 108 beats per minute. The fact that the elevated heart rate occurred 4 days after receiving treatment A makes this AE unlikely to be related to the study drug. Vital signs did not reveal any specific or clinically significant safety findings.*

### **Electrocardiograms (ECGs)**

ECG was collected at baseline and at EOS visit for all patients. The Applicant reports no clinically significant abnormal ECG results during the study.

**QT**

Not applicable

**Immunogenicity**

Not applicable

**Physical Exam**

One subject had clinically significant physical exam findings:

- Subject (b) (6) had cellulitis of the left leg. The details of this subject's care were provided above under analysis by Treatment group.

*Reviewer Comment: Physical exam findings did not reveal any specific or clinically significant safety findings. Leg pain and cellulitis findings in one subject were unlikely related to the drug products.*

**7.2.5. Analysis of Submission-Specific Safety Issues**

None

**7.2.6. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability**

Not applicable

**7.2.7. Safety Analyses by Demographic Subgroups**

Not applicable

**7.2.8. Specific Safety Studies/Clinical Trials**

Not applicable

**7.2.9. Additional Safety Explorations**

**Human Carcinogenicity or Tumor Development**

Not applicable

**Human Reproduction and Pregnancy**

Except for urine pregnancy tests obtained in screening of subjects, no human reproduction or additional pregnancy data was included in this NDA submission.

### **Pediatrics and Assessment of Effects on Growth**

There was no assessment of effects on pediatric growth in this NDA. Refer to Section [9](#) for review of pediatric assessment under the Pediatric Research and Equity Act (PREA).

### **Overdose, Drug Abuse Potential, Withdrawal, and Rebound**

The proposed drug product is an ER combination product containing 30 mg of dextromethorphan HBr. Due to the established abuse potential of dextromethorphan, the Controlled Substance Staff (CSS) was consulted to evaluate the abuse and misuse potential of dextromethorphan in this formulation.

Dr Chad Reissig from CSS conducted a comprehensive evaluation and concluded that the proposed drug product does not present an increased abuse potential relative to existing FDA approved products containing dextromethorphan. Based on this assessment, no specific regulatory actions or additional labeling information were recommended to address misuse and abuse potential concerns.

For additional details regarding this evaluation, refer to Section 7.7.3 of the Integrated Review dated July 26, 2024, and to CSS consult memorandum by Dr Chad Reissig dated January 22, 2024 (DARRTS Reference ID: 5314327).

## **7.2.10. Safety in the Postmarket Setting**

### **Safety Concerns Identified Through Postmarket Experience**

Refer to Section 7.6.2. of the Integrated Review dated July 26, 2024 (for extensive review of the postmarketing data submitted for this drug product).

### **Expectations on Safety in the Postmarket Setting**

Refer to Section 7.6.2. of the Integrated Review dated July 26, 2024 (for extensive review of the postmarketing data submitted for this drug product).

## **7.3. Conclusions and Recommendations**

The safety evaluation of this new FDC consisted of a comprehensive evaluation of four clinical studies (two pivotal and two pilot clinical pharmacology studies) and a review of postmarketing surveillance data from multiple sources including FAERS, WHO Vigibase, Applicant's internal safety database, NPDS and literature review.

The integrated safety analysis did not identify any new or unexpected safety signals that would preclude nonprescription use of this product in adults and children 12 years and older. The benefit-risk assessment remains favorable for the proposed indications.

NDA/BLA Multi-disciplinary Review and Evaluation {NDA 217338}

{guaifenesin/dextromethorphan hydrobromide/naproxen sodium tablets}

The Division of Nonprescription Drugs 1 recommends approval of this application from a safety perspective. The totality of evidence supports the safe use of this FDC product for the proposed nonprescription indications when used according to the proposed labeling.

## **8 Advisory Committee Meeting and Other External Consultations**

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

## 9 Pediatrics

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Pediatric Research and Equity Act (PREA) was triggered for this submission because the proposed product represents a new fixed dose combination product. The Applicant submitted an initial Pediatric Study Plan (iPSP) that proposed a request for a pediatric waiver in children less than 12 years and extrapolation to support use in children 12 years and older. This was discussed by the Pediatric Research Committee (PeRC) on January 23, 2019, and the Applicant received an agreed PSP on June 1, 2019.

In this current submission, 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 has also requested a partial waiver for children 4 to less than 12 years of age and FDA agreed to this partial waiver because the product would not represent a meaningful therapeutic benefit.

The Applicant proposed to use identical dosing instructions for adolescents (12 to less than 17 years) and adults. This would mirror the dosing directions of the cross-reference drug Mucinex DM and the listed drug Aleve, which are both approved for use in children 12 years and older with the same directions as for adults. The pediatric assessment relies 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 FDC component with its corresponding cross-reference or listed drug (Mucinex DM or Aleve), the adult PK data can be extrapolated to support safety and efficacy in the pediatric population down to 12 years without requiring additional pediatric studies.

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.

The proposed labeling for this product includes the contraindication, “Do not use” for children under 12 years of age.

The PeRC meeting was held on November 4, 2025, and deemed the pediatric study plan acceptable.

## 10. Labeling Assessments

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### 10.1. Nonprescription Drug Labeling

The Applicant submitted outer carton and immediate container (blister) labeling for its proposed drug (see [Table 11](#)). The proposed labeling reflects aspects of the approved labeling for NDA 021620 (Mucinex DM), NDA 021076 (Aleve-D Sinus and Cold), and NDA 020204 (Aleve) given this application relies on the safety and efficacy from these NDAs.

The interdisciplinary scientist review team in the Division of Nonprescription Drugs 1 (DNPD I) was tasked with assessing the labeling proposed in NDA 217338 to determine if it:

1. Follows nonprescription labeling regulations,
2. Makes truthful and non-misleading claims,
3. Appropriately integrates requirements for naproxen sodium nonprescription labeling.

The proposed draft labeling for the product was assessed to determine whether it was presented in accordance with all applicable regulations<sup>15</sup>. The review team identified minor labeling issues that are summarized below. The Applicant was notified of these issues in the October 15, 2025, Information Request letter. The Applicant resolved these issues in its October 24, 2025, submission.

#### **Summary of Labeling Issues Identified**

##### **Principal Display Panel (PDP):**

- The proprietary name, "Mucinex 12HR Cold & Fever Multi-Symptom," was not consistently prominent. The term "Multi-Symptom" appeared as a descriptor rather than part of the proprietary name due to inconsistent type sizing.
- The statement of identity (SOI) formatting did not comply with bold face type requirements under 21 CFR 201.61(c).
- "Value-size" promotional flags were inconsistently used across different package sizes without clear justification.
- Inconsistent placement of "Bi-Layer Tablets" term across different count sizes.

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<sup>15</sup> 21 CFR 201.60 – 201.80; Draft guidance for industry Statement of Identity and Strength — Content and Format of Labeling for Human Nonprescription Drug Products (September 2022)

**Drug Facts Label (DFL) Regulatory Compliance Issues:**

- Incorrect use of singular “**Purpose**” heading instead of required plural “**Purposes**” form per 21 CFR 201.66(c)(3).
- Improper footnote formatting using (b) (4) instead of an asterisk for the term “NSAID.” Per 21 CFR 201.326(a)(2)(ii), the Active ingredients section must contain the term “(NSAID\*)” after the naproxen sodium active ingredient, where an asterisk immediately follows the term “NSAID” to direct the consumer to the full term “Nonsteroidal anti-inflammatory drug.”

**Drug Facts Label (DFL) Clinical Concern:**

- The allergy warning was not positioned as the first bullet point under “**Do not use**” subheading.

**Table 11. Proposed Draft Labeling**

| Proposed Labeling                        | Dates Submitted                                                       |
|------------------------------------------|-----------------------------------------------------------------------|
| 4-count outer carton (HCP sample)        | September 29, 2023, February 22, 2024, July 7, 2025, October 24, 2025 |
| 8-count outer carton                     | September 29, 2023, February 22, 2024, July 7, 2025, October 24, 2025 |
| 16-count outer carton                    | September 29, 2023, February 22, 2024, July 7, 2025, October 24, 2025 |
| 32-count outer carton                    | September 29, 2023, February 22, 2024, July 7, 2025, October 24, 2025 |
| 60-count outer carton                    | September 29, 2023, February 22, 2024, July 7, 2025, October 24, 2025 |
| 4-count blister card                     | September 29, 2023, February 22, 2024, July 7, 2025                   |
| 8-count blister card                     | September 29, 2023, February 22, 2024, July 7, 2025                   |
| 10-count blister card                    | September 29, 2023, February 22, 2024, July 7, 2025                   |
| 4-count peel-back DFL                    | September 29, 2023, February 22, 2024, July 7, 2025, October 24, 2025 |
| 8-, 16-, 32-, and 60-count peel-back DFL | September 29, 2023, February 22, 2024, July 7, 2025, October 24, 2025 |

|                  |                  |
|------------------|------------------|
| Website mock-ups | October 24, 2025 |
|------------------|------------------|

Source: Reviewer generated table using labeling materials from NDA Module 1.14.1.1 submitted September 29, 2023, February 22, 2024, July 7, 2025, and October 24, 2025.

Abbreviations: DFL, Drug Facts label; HCP, health care professional

**Figure 2. Outer Carton**



Source: NDA 217338 submitted October 24, 2025

## 10.2. Drug Facts Label

The proposed Drug Facts label (DFL) is presented in two peel-back labels, one label will be contained on the 4-count outer carton label and the other label will be used on the 8-count, 16-count, 32-count, and 60-count outer carton labels ([Figure 3](#)). Both proposed peel back presentations display the “**Drug Facts**” title, “**Active ingredient**” heading, and “**Purpose**” headings without needing to peel back the label. A statement instructing the consumer to “PEEL CORNER FOR COMPLETE DRUG FACTS” is contained in the lower left corner of the first page of the label. The proposed DFL is acceptable.

The proposed directions (listed below) specify a dosing regimen of two tablets every 12 hours for adults and children 12 years and older. The proposed dosage form is a bilayer tablet that contains 30 mg of dextromethorphan HBr, 600 mg of guaifenesin, and 110 mg of naproxen sodium. The proposed product matches the active ingredient strengths and dosing instructions

of Mucinex DM (NDA 021620), which contains identical amounts of dextromethorphan HBr and guaifenesin per tablet. For the naproxen sodium component, each tablet of the proposed product contains 110 mg, which is half the strength of Aleve tablets (NDA 020204) that contain 220 mg naproxen sodium. While Aleve dosing is one tablet every 8 to 12 hours, the proposed product requires two tablets every 12 hours.

- do not crush, chew, or break extended-release tablet
- do not take more than directed
- take each dose with a full glass of water
- adults and children 12 years and older: take 2 extended-release tablets every 12 hours; not more than 4 extended-release tablets in 24 hours
- children under 12 years of age: do not use

The proposed indications (below) are consistent with the reference drugs.

- helps loosen phlegm (mucus) and thin bronchial secretions to rid the bronchial passageways of bothersome mucus and make coughs more productive,
- temporarily relieves
  - cough due to minor throat and bronchial irritation as may occur with the common cold or inhaled irritants
  - the intensity of coughing
  - the impulse to cough to help you get to sleep
  - minor aches and pains due to headache and the common cold
- temporarily reduces fever

The warnings contained in the Drug Facts label (DFL) are consistent with class labeling for dextromethorphan HBr, guaifenesin, and naproxen sodium.

**Figure 3. Proposed Drug Facts Label**

**Peel-back label for 8-ct, 16-ct, 32-ct, and 60-ct outer carton labels**





Source: NDA 217338 submitted October 24, 2025

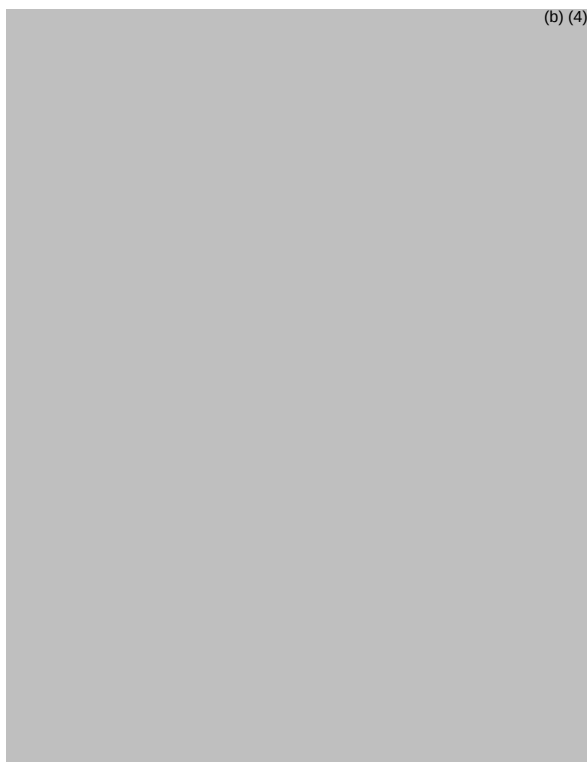
### **10.3. Principal Display Panel**

A new proprietary name was submitted for review on July 11, 2025, Mucinex 12HR Cold & Fever Multi-Symptom. DMEPA reviewed the proposed name for safety and misbranding concerns. They found that the proposed name with the modifier “Cold & Fever Multi-Symptom” is conditionally acceptable (Correspondence to the Applicant dated September 18, 2025).

The proposed proprietary name is located in the upper center of the PDP. The content of the required elements of the PDP, the statement of identity (SOI), proprietary name placement and size, and net quantity statement, are compliant with the requirements under 21 CFR 201.60-201.62 ([Figure 4](#)).

The branding of Mucinex products include a subdued 'M' logo that serves as a background design element on the bottom half of the PDP. Each individual product line uses a distinct color for branding to help consumers distinguish between the product lines at the point of purchase (e.g., Mucinex, Mucinex DM, Mucinex Sinus Max, and the proposed product Mucinex 12HR Cold & Fever Multi-Symptom). The color of the branding for this proposed product is light gray.

**Figure 4. Proposed PDP for 16-Count Outer Carton**



Source: NDA 217338 submitted October 24, 2025

#### **10.4. Blister Package Labeling**

The Applicant provided labeling for three immediate container (blister) configurations: 4-count, 8-count, and 10-count cards. The 8-count blister labeling doubles the 4-count card design, and the 10-count labeling doubles a 5-count card design. The same 8-count blister card is used in the 8-, 16-, and 32-count cartons. The 60-count carton contains six 10-count blister cards.

Each blister has a back label containing important information for the consumer. Labels for blisters that contain drug product display the following information: proprietary name, active ingredients, distributor information, country of origin, and a statement to “See warnings before use.”

The 4-count blister mats contain two center panels that do not contain drug product ([Figure 5](#)). The top panel displays the proprietary name, SOI, and lot numbering. The lower panel contains the statement, “Keep this warning. Do not detach individual blisters until ready to use,” and the NSAID stomach bleeding warning. This warning must appear on both outer and immediate container labels, per 21 CFR 326(a)(2)(iii)(A).

The 10-count blister mats (i.e., two 5-count mats) contains five blisters with drug product, replacing the top center panel with a panel that contains drug product ([Figure 5](#)). The NSAID stomach bleeding warning is contained on the lower center panel.

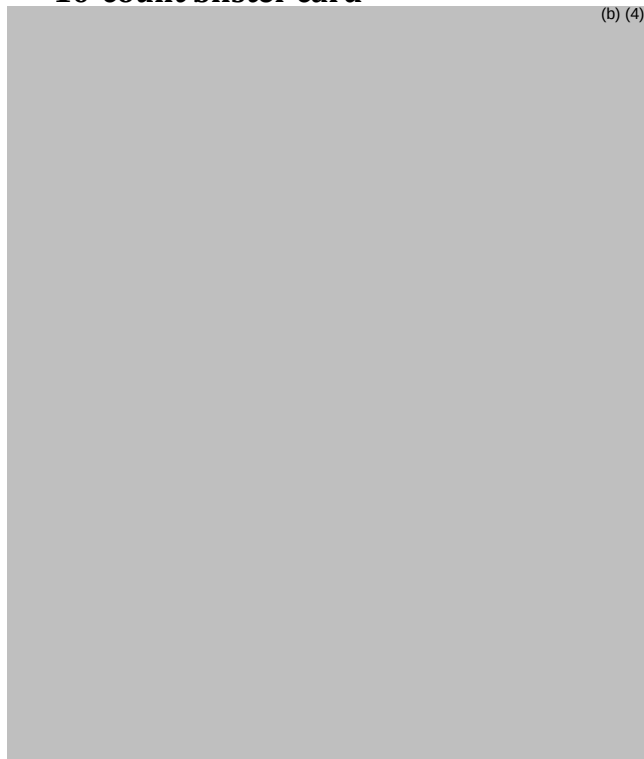
**Figure 5. Immediate Container (Blister Mat) Labeling**

**4-count blister card**



Source: NDA 217338 submitted July 7, 2025

**10-count blister card**



Source: NDA 217338 submitted July 7, 2025

### **10.5. Review of Website Mock-Ups**

Because the website address [www.mucinex.com](http://www.mucinex.com) is included on the labeling, the Applicant was requested to submit mock-ups of the proposed webpages for the Mucinex 12HR Cold & Fever Multi-Symptom product. These mock-ups were requested in an Information Request letter dated October 15, 2025. This content was found to be acceptable and is consistent with the proposed product labeling.

### **10.6. Conclusions**

The Division of Nonprescription Drugs 1 recommends approval of this application regarding labeling. The content of the proposed labeling is presented in accordance with all applicable regulations. The labeling issues that were identified in the October 15, 2025, information request were sufficiently addressed by the Applicant and no additional labeling issues have been identified.

## **11 Risk Evaluation and Mitigation Strategies (REMS)**

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None

## **12 Postmarketing Requirements and Commitment**

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Routine postmarketing surveillance is sufficient to monitor adverse events, particularly focusing on respiratory depression and any unexpected adverse events.

### **13 DNPDI Division Director/Signatory Comments**

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I concur with the review team's assessment and recommendations for this resubmission of NDA 217338.

The regulatory action is Approval with the agreed-upon labeling.

No PMR/PMCs are recommended for this NDA.

## 14 Appendices

### 14.1. References

References are placed in footnotes under the unireview text.

### 14.2. Financial Disclosure

**Covered Clinical Study (Name and/or Number):** Clinical Study RB5-US-1505 and Study 0225104

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                                         |                                                              |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------|--------------------------------------------------------------|
| Was a list of clinical investigators provided:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | Yes <input checked="" type="checkbox"/> | No <input type="checkbox"/> (Request list from Applicant)    |
| Total number of investigators identified: <u>22</u>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                         |                                                              |
| 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): <u>0</u>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                         |                                                              |
| <p>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)):</p> <p>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____</p> <p>Significant payments of other sorts: _____</p> <p>Proprietary interest in the product tested held by investigator: _____</p> <p>Significant equity interest held by investigator in S</p> <p>Sponsor of covered study: _____</p> |                                         |                                                              |
| Is an attachment provided with details of the disclosable financial interests/arrangements:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | Yes <input type="checkbox"/>            | No <input type="checkbox"/> (Request details from Applicant) |
| Is a description of the steps taken to                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | Yes <input type="checkbox"/>            | No <input type="checkbox"/> (Request information             |

|                                                                                          |                              |                                                                  |
|------------------------------------------------------------------------------------------|------------------------------|------------------------------------------------------------------|
| minimize potential bias provided:                                                        |                              | from Applicant)                                                  |
| Number of investigators with certification of due diligence (Form FDA 3454, box 3) _____ |                              |                                                                  |
| Is an attachment provided with the reason:                                               | Yes <input type="checkbox"/> | No <input type="checkbox"/> (Request explanation from Applicant) |

### 14.3. Nonclinical Pharmacology/Toxicology

Not applicable

### 14.4. OCP Appendices (Technical Documents Supporting OCP Recommendations)

#### 14.4.1. Study Design, Analysis Plan and Demographics of Study 0225104

##### Study Design and Treatments

Study 0225104 was a phase 1, open-label, single-dose, randomized, 2-way crossover relative bioavailability study conducted to address the CRL deficiency regarding the 12-hour dosing interval for naproxen. The primary objective was to assess the relative bioavailability of immediate-release naproxen sodium component from the proposed product relative to listed drug, Aleve-D Sinus and Cold (NDA 021076) under fasted conditions.

We note that the study utilized the current Orange Book reference standard (ANDA 076518) as the reference treatment arm given that NDA 021076 (Aleve-D Sinus and Cold) has been discontinued currently. This discontinuation was not due to safety or efficacy reasons. This study design approach was agreed upon by the FDA during pre-study discussions, as documented in the preliminary meeting comments dated October 28, 2024 (Reference ID: 5469432).

Twenty-six healthy subjects were enrolled and completed both treatment periods with a 5-day washout:

- Treatment A: Two (b) (4) tablets (total 220 mg naproxen sodium) after 10-hour fast
- Treatment B: One Aleve-D Sinus and Cold tablet (ANDA 076518, 220 mg naproxen sodium) after 10-hour fast

##### PK Sampling and Analysis

Blood samples were drawn pre-dose and at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 6, 8, 9, 10, 11, 12, 18, 24, 48, and 72 hours post-dose. Noncompartmental analysis was performed using Phoenix WinNonlin (version 8.3.4).

### **Study Demographic**

The study population consisted of 19 male participants (73.1%) and 7 female participants (26.9%), with all female participants being of childbearing potential. The majority of participants were White (76.9%) with 23.1% Black or African American. All participants (100%) were Hispanic or Latino ethnicity. The mean age was 31.3 years (range 21-41 years), mean height was 1.739 m (range 1.58-1.93 m), mean weight was 77.15 kg (range 52.3-99.5 kg), and mean BMI was 25.35 kg/m<sup>2</sup> (range 19.0-30.0 kg/m<sup>2</sup>).

### **The Study Completion, Discontinuation, and Protocol Deviations**

A total of 62 healthy participants were screened for eligibility, with 41 participants enrolled and 26 participants randomized and dosed. Of the 36 participants (58.1%) not randomized, 28 participants (45.2%) did not meet study criteria and 8 participants (12.9%) were excluded for other reasons. No participants were excluded due to adverse events, protocol violations, or withdrawal of consent.

All 26 randomized participants (100%) completed both treatment periods, and all required pharmacokinetic sampling through 72 hours post-dose in each period. Two participants (7.7%) were lost to follow-up as they did not return for the final study visit, resulting in 24 participants (92.3%) completing the entire study. These participants had completed all treatment periods and pharmacokinetic sampling, missing only the final safety follow-up visit. All 26 randomized participants were included in the Safety Population, PK Population, and Per Protocol PK Population.

In Treatment group B, there was one subject with protocol deviation. The deviation involved failure to perform or document the lymph node assessment at screening visit. A repeat assessment of lymph nodes showed no abnormalities, and the participant was not excluded from the Per Protocol PK Population.

Based on the protocol deviation listings (Listing 16.2.2.2), 36 other protocol deviations were reported which were designated as non-important. These were primarily related to vital signs timing issues (26 instances where vital signs were collected 21-34 minutes outside the required 90±15 minute pre-dose window), vital signs documentation problems (8 instances where resting position was not documented), and minor procedural issues including use of different arms for measurements and one blood sample collected 2 minutes outside the acceptable window.

### **Safety Results**

No deaths, serious adverse events, or discontinuations due to adverse events occurred. Seven participants (26.9%) reported 15 treatment-emergent adverse events during the study. Four participants (15.4%) reported 7 events after receiving (b) (4), and 5 participants (19.2%) reported 8 events after receiving Aleve-D Sinus and Cold. Thirteen events were mild in severity

and 2 events in 1 participant were moderate. None of the adverse events were considered related to (b) (4), and 1 event was considered possibly related to Aleve-D Sinus and Cold.

The Applicant's study design for Study 0225104 was adequate. Refer to Section 7 in this review for detail safety assessment.

#### 14.4.2. Bioanalytical Method Validation and Performance

The bioanalytical method and report for Study RB5-US-1505 was previously reviewed during the first submission of NDA 217338 and found to be adequate; refer to Section 14.3 of the Integrated Review for that study for detailed assessment.

For bioanalysis of the PK samples from Study 0225104, a liquid chromatography-tandem mass spectrometry (LC-MS/MS) assay was used. This method determines the concentration of naproxen in K2EDTA human plasma. It was developed and validated by (b) (4) according to test method TM.2956 over an analytical range of 1 to 200 µg/mL. The method was reasonably validated in accordance with current FDA bioanalytical method validation guidelines, demonstrating acceptable accuracy (bias within ±15% for QC levels and ±20% for LLOQ), precision (CV ≤15% for QC levels and ≤20% for LLOQ), selectivity, stability, and method reproducibility with 100% of incurred sample reanalysis samples meeting acceptance criteria.

**Table 12. Summary of Method Validation for the Determination of Naproxen in Human Plasma in Study 0225104**

| Study Information                      | Method Validation Summary                                                                                                                                                                              |
|----------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Method Validation Summary Report Title | Validation of a Liquid Chromatographic Method using Tandem Mass Spectrometry Detection and Automated Extraction for the Determination of Naproxen (1 to 200 µg/mL) in Human EDTA K <sub>2</sub> Plasma |
| Study Number                           | 205134AXWU                                                                                                                                                                                             |
| Test Method                            | TM.2956                                                                                                                                                                                                |
| Analyte Name                           | Naproxen                                                                                                                                                                                               |
| Internal Standard                      | Naproxen-d <sub>3</sub>                                                                                                                                                                                |
| Sample Volume                          | 0.05 mL                                                                                                                                                                                                |
| QC Concentrations                      | 1.00, 3.00, 100.00, and 150.00 µg/mL                                                                                                                                                                   |
| Standard Curve Concentrations          | 1.00, 2.00, 10.00, 20.00, 40.00, 80.00, 160.00, and 200.00 µg/mL                                                                                                                                       |

NDA/BLA Multi-disciplinary Review and Evaluation {NDA 217338}  
{guaifenesin/dextromethorphan hydrobromide/naproxen sodium tablets}

|                                                      |                                                                                               |
|------------------------------------------------------|-----------------------------------------------------------------------------------------------|
| <b>Lower Limit of Quantitation</b>                   | 1.00 µg/mL                                                                                    |
| <b>Upper Limit of Quantitation</b>                   | 200.00 µg/mL                                                                                  |
| <b>Calibration Range</b>                             | 1.00 to 200 µg/mL                                                                             |
| <b>Calibration Curve Regression</b>                  | Linear                                                                                        |
| <b>Weighting Factor</b>                              | 1/C <sup>2</sup>                                                                              |
| <b>Mean Recovery of Analyte (%)</b>                  | 75.03, 73.13, and 74.63% (at QC1, QC2, and QC3 levels)                                        |
| <b>Mean Recovery of Internal Standard (%)</b>        | 76.07%                                                                                        |
| <b>Matrix Effect CV (%)</b>                          | ≤1.15%                                                                                        |
| <b>Sensitivity</b>                                   | The accuracy at LLOQ was within ±20.0% of nominal values. The %CV at LLOQ was less than 20.0% |
| <b>LLOQ QC Intra-Run Precision Range (%CV)</b>       | 3.78 to 8.93%                                                                                 |
| <b>LLOQ QC Intra-Run Accuracy Range (%RE)</b>        | -8.08 to 0.17%                                                                                |
| <b>Analytical QC Intra-Run Precision Range (%CV)</b> | 0.87 to 8.65%                                                                                 |
| <b>Analytical QC Intra-Run Accuracy Range (%RE)</b>  | -19.67 to 3.49%                                                                               |
| <b>LLOQ QC Inter-Run Precision (%CV)</b>             | 8.93%                                                                                         |
| <b>LLOQ QC Inter-Run Accuracy (%RE)</b>              | -8.08%                                                                                        |
| <b>Analytical QC Inter-Run Precision Range (%CV)</b> | 3.78 to 8.93%                                                                                 |
| <b>Analytical QC Inter-Run Accuracy Range (%RE)</b>  | -8.08 to 0.17%                                                                                |
| <b>Stock Solution Stability</b>                      | 1630 days at -20°C                                                                            |
| <b>Processed Sample Stability</b>                    | 95h20min at room temperature                                                                  |
| <b>Benchtop Stability in Plasma</b>                  | 23h46min at room temperature and 24h08min at 4°C                                              |

|                                              |                                                                                            |
|----------------------------------------------|--------------------------------------------------------------------------------------------|
| <b>Freeze/Thaw Stability in Plasma</b>       | 4 cycles at -20°C and -80°C                                                                |
| <b>Benchtop Stability in Whole Blood</b>     | 240 minutes in ice/water bath (centrifugation at room temperature and at 4°C)              |
| <b>Long-term Storage Stability in Plasma</b> | 6 and 1618 days at -20°C; 6 days at -80°C                                                  |
| <b>Dilution Integrity</b>                    | 20-fold dilution validated                                                                 |
| <b>Selectivity</b>                           | No significant interference observed in 8 out of 8 tested matrices for naproxen and its IS |
| <b>Specificity</b>                           | No significant interference observed with acetaminophen                                    |
| <b>Matrix Effect</b>                         | Mean IS-Normalized matrix factor: 0.996040 and 1.009345; CV: 0.82% and 1.15%               |
| <b>Carryover</b>                             | No significant carryover observed                                                          |

Source: Study 0225104 Bioanalytical Method Validation Report<sup>16</sup>

Abbreviations: C, Celsius; CV, coefficient of variation; IS, internal standard; ISR, incurred sample reanalysis; LC-MS/MS, liquid chromatography with tandem mass spectrometry; LLOQ, lower limit of quantification; mL, milliliter; QC, quality control; %RE, relative error; µg, microgram

**Table 13. Summary of In-Study Performance of LC-MS/MS Method for the Determination of Naproxen in Human Plasma in Study 0225104**

| <b>Performance Parameters</b>           | <b>Results</b>                                                                                    |
|-----------------------------------------|---------------------------------------------------------------------------------------------------|
| <b>Assay Passing Rate</b>               | Data from incurred sample reproducibility (ISR) showed 100.00% of samples met acceptance criteria |
| <b>Standard Calibration Curve</b>       | 8 calibration standards from 1.00 to 200.00 µg/mL                                                 |
| <b>Standard Calibration Performance</b> | Cumulative bias range: -1.49% to 1.83%                                                            |

<sup>16</sup> [\\CDSESUB1\EVSPROD\nda217338\0025\m5\53-clin-stud-rep\531-rep-biopharm-stud\5314-bioanalyt-analyt-met\0225104\0225104-val-rpt.pdf](#)

|                                         |                                                                                                                                                        |
|-----------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>QC Performance</b>                   | Cumulative bias range: -8.08% to 0.17%; Cumulative precision: ≤8.93% CV                                                                                |
| <b>Method Reproducibility</b>           | ISR was performed and 100.00% of samples met the pre-specified acceptance criteria (percentage difference within ±20% for at least 67% of ISR samples) |
| <b>Sample Analysis and Storage Time</b> | All samples were analyzed within established long-term storage stability periods                                                                       |

Source: Study 0225104 Bioanalytical Report<sup>17</sup>

Abbreviations: C, Celsius; CV, coefficient of variation; IS, internal standard; ISR, incurred sample reanalysis; LC-MS/MS, liquid chromatography with tandem mass spectrometry; LLOQ, lower limit of quantification; mL, milliliter; QC, quality control; %RE, relative error; µg, microgram

### 14.4.3. Summary of OSIS inspection

On July 14, 2025, a request for biopharmaceutical inspections was issued to Office of Study Integrity and Surveillance (OSIS) for two sites supporting the clinical study and bioanalysis of Study #0225104 for this resubmission<sup>18</sup>:

- Clinical Site: Syneos Health Clinical Research Services, LLC; Miami, FL
- Analytical site: (b) (4)

OSIS declined to conduct the requested on-site inspection of the clinical site at Syneos Health Clinical Research Services, LLC (Miami, FL) based on a recent August 2024 inspection conducted under NDA (b) (4) non-responsive (b) (4).

(b) (4) however, OSIS determined that these findings did not compromise data integrity or subject safety. Accordingly, OSIS concluded that no additional inspection of this clinical site is warranted for the current submission<sup>19</sup>.

OSIS also declined to conduct the requested on-site inspection of the bioanalytical facility at (b) (4) based on a recent (b) (4) inspection conducted under multiple NDAs (b) (4) non-responsive (b) (4)). OSIS

<sup>17</sup> [\\CDSESUB1\EVSPROD\nda217338\0025\m5\53-clin-stud-rep\531-rep-biopharm-stud\5314-bioanalyt-analyt-met\0225104\0225104-bio-rpt.pdf](#)

<sup>18</sup> OSIS Consult Request for Biopharmaceutical Inspections; DARRTS Reference ID: 5623851

<sup>19</sup> Decline to conduct an on-site inspection for NDA 217338 Clinical Site at Syneos Health Clinical Research Services, LLC; Miami, FL; OSIS Memorandum; DARRTS Reference ID: 5649141

concluded that the data from studies conducted at this facility were reliable and determined that no additional inspection of the bioanalytical site is warranted for NDA 217338<sup>20</sup>.

---

<sup>20</sup> Decline to conduct an on-site inspection for NDA217338 Analytical Site at [REDACTED] (b) (4)  
[REDACTED]; OSIS Memorandum; Reference ID: 5708749

-----  
**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  
12/22/2025 03:45:44 PM

YUNZHAO REN  
12/22/2025 05:16:30 PM

NUSHIN F TODD  
12/22/2025 05:17:01 PM

**Integrated Review****Table 1. Application Information**

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

<sup>1</sup> For internal tracking purposes only.

Abbreviations: PDUFA, Prescription Drug User Fee Act; SNOMED CT, Systematized Nomenclature of Medicine Clinical Terms

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Guaifenesin/dextromethorphan hydrobromide/naproxen sodium tablets

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## Glossary

|                    |                                                                                 |
|--------------------|---------------------------------------------------------------------------------|
| ADAM               | advanced dissolution, absorption, and metabolism                                |
| AE                 | adverse event                                                                   |
| AUC                | area under the concentration-time curve                                         |
| AUC <sub>inf</sub> | area under the concentration-time curve estimated to infinity                   |
| AUC <sub>0-t</sub> | 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 <sub>iv</sub>   | plasma clearance                                                                |
| C <sub>max</sub>   | 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 <sub>max</sub>   | time to maximum concentration                                                   |
| USP                | United States Pharmacopeia                                                      |
| VBE                | virtual bioequivalent                                                           |
| V <sub>ss</sub>    | volume of distribution                                                          |
| WHO                | World Health Organization                                                       |

# I. Executive Summary

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## 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 | <ul style="list-style-type: none"> <li>The common cold is one of the most frequently occurring illnesses that affect millions of Americans annually (<a href="#">Heikkinen and Järvinen 2003</a>).</li> <li>Colds can be caused by more than 200 different respiratory viruses (<a href="#">Eccles 2023</a>).</li> <li>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 (<a href="#">Eccles 2023</a>).</li> <li>Symptoms of the common cold may include cough, mucus production, minor aches and pains, headache, and fever among other symptomatology.</li> <li>Though they are self-limited and generally not considered a serious medical condition, colds can be bothersome to consumers and affect quality of life.</li> <li>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 (<a href="#">Fendrick et al. 2003</a>).</li> </ul> | <ul style="list-style-type: none"> <li>The common cold affects millions of Americans annually.</li> <li>Symptoms caused by the common cold can be uncomfortable and can temporarily affect quality of life.</li> <li>Symptoms associated with the common cold are generally self-diagnoseable and self-manageable for lay consumers.</li> </ul> |

NDA 217338

Guaifenesin/dextromethorphan hydrobromide/naproxen sodium tablets

| Dimension                 | Evidence and Uncertainties                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | Conclusions and Reasons                                                                                                                                                                                                                                                                                    |
|---------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Current treatment options | <ul style="list-style-type: none"><li>• 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.</li><li>• 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.</li></ul> | <ul style="list-style-type: none"><li>• Consumers rely on available safe and effective nonprescription drugs for symptomatic relief of symptoms associated with the common cold.</li><li>• A variety of treatment options is currently available for multisymptom management of the common cold.</li></ul> |

| Dimension | Evidence and Uncertainties                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | Conclusions and Reasons                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
|-----------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Benefit   | <ul style="list-style-type: none"> <li>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.</li> <li>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.</li> <li>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.</li> <li>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.</li> <li>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.</li> </ul> | <ul style="list-style-type: none"> <li>The proposed FDC product would present consumers with another alternative for nonprescription management of symptoms caused by the common cold.</li> <li>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.</li> </ul> |

| Dimension                | Evidence and Uncertainties                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | Conclusions and Reasons                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|--------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Risk and risk management | <ul style="list-style-type: none"> <li>Single ingredient products containing guaifenesin, dextromethorphan HBr, and naproxen sodium have been marketed as nonprescription drugs for decades.</li> <li>The safety profile for each active ingredient is well characterized.</li> <li>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.</li> <li>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.</li> <li>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.</li> </ul> | <ul style="list-style-type: none"> <li>There were no SAEs or significant safety findings from the clinical program for this FDC product.</li> <li>There were no significant findings in the postmarketing safety data when looking at concomitant use of all three active ingredients.</li> <li>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.</li> </ul> |

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

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### 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) 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 | <ul style="list-style-type: none"> <li>Ibuprofen 200 mg</li> <li>Pseudoephedrine HCl 30 mg</li> </ul> | <ul style="list-style-type: none"> <li>Pain reliever/fever reducer</li> <li>Nasal decongestant</li> </ul> | Oral capsule:<br>1 capsule every 4 – 6 hours |

| Product Name           | Active Ingredients and Dose                                                                                  | Purpose                                                                                                   | Route, Dosage Form, and Dosing Instructions |
|------------------------|--------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------|---------------------------------------------|
| Advil Cold and Sinus   | <ul style="list-style-type: none"> <li>Ibuprofen 200 mg</li> <li>Pseudoephedrine HCl 30 mg</li> </ul>        | <ul style="list-style-type: none"> <li>Pain reliever/fever reducer</li> <li>Nasal decongestant</li> </ul> | Oral caplet:<br>1 caplet every 4 – 6 hours  |
| Aleve-D Sinus and Cold | <ul style="list-style-type: none"> <li>Naproxen sodium 220 mg</li> <li>Pseudoephedrine HCl 120 mg</li> </ul> | <ul style="list-style-type: none"> <li>Pain reliever/fever reducer</li> <li>Nasal decongestant</li> </ul> | Oral caplet:<br>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                          | <ul style="list-style-type: none"> <li>Pain reliever/fever reducer</li> <li>Cough suppressant</li> </ul>                             | Tablet, capsule, solution |
| Acetaminophen, Chlorpheniramine maleate                      | <ul style="list-style-type: none"> <li>Pain reliever/fever reducer</li> <li>Antihistamine</li> </ul>                                 | Tablet, capsule           |
| Acetaminophen, Guaifenesin                                   | <ul style="list-style-type: none"> <li>Pain reliever/fever reducer</li> <li>Expectorant</li> </ul>                                   | Capsule, solution         |
| Acetaminophen, Dextromethorphan HBr, Guaifenesin             | <ul style="list-style-type: none"> <li>Pain reliever/fever reducer</li> <li>Cough suppressant</li> <li>Expectorant</li> </ul>        | Capsule, solution         |
| Acetaminophen Dextromethorphan HBr, Doxylamine succinate     | <ul style="list-style-type: none"> <li>Pain reliever/fever reducer</li> <li>Cough suppressant</li> <li>Antihistamine</li> </ul>      | Tablet, capsule, solution |
| Acetaminophen Dextromethorphan HBr, Chlorpheniramine maleate | <ul style="list-style-type: none"> <li>Pain relief/ fever reducer</li> <li>Cough suppressant</li> <li>Antihistamine</li> </ul>       | Tablet, solution          |
| Acetaminophen Dextromethorphan HBr, Diphenhydramine          | <ul style="list-style-type: none"> <li>Pain relief/ fever reducer</li> <li>Cough suppressant</li> <li>Antihistamine</li> </ul>       | Solution                  |
| Acetaminophen Dextromethorphan HBr, Pseudoephedrine HCl      | <ul style="list-style-type: none"> <li>Pain reliever/fever reducer</li> <li>Cough suppressant</li> <li>Nasal decongestant</li> </ul> | Tablet                    |

| Active Ingredients                                                              | Purpose                                                                                                                                                             | Dosage Form(s) |
|---------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------|
| Acetaminophen Dextromethorphan<br>HBr, Chlorpheniramine,<br>Pseudoephedrine HCl | <ul style="list-style-type: none"> <li>• Pain reliever/fever reducer</li> <li>• Cough suppressant</li> <li>• Antihistamine</li> <li>• Nasal decongestant</li> </ul> | Tablet         |
| Acetaminophen Dextromethorphan<br>HBr, Guaifenesin, Pseudoephedrine<br>HCl      | <ul style="list-style-type: none"> <li>• Pain reliever/fever reducer</li> <li>• Cough suppressant</li> <li>• Expectorant</li> <li>• Nasal decongestant</li> </ul>   | 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**

| <b>Data Submitted in the Application</b>                                  |                                                                                                                              |                                               |
|---------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------|
| <b>Check if Submitted</b>                                                 | <b>Type of Data</b>                                                                                                          | <b>Section Where Discussed, if Applicable</b> |
| <b>Clinical Outcome Assessment Data Submitted in the Application</b>      |                                                                                                                              |                                               |
| <input type="checkbox"/>                                                  | Patient-reported outcome                                                                                                     |                                               |
| <input type="checkbox"/>                                                  | Observer-reported outcome                                                                                                    |                                               |
| <input type="checkbox"/>                                                  | Clinician-reported outcome                                                                                                   |                                               |
| <input type="checkbox"/>                                                  | Performance outcome                                                                                                          |                                               |
| <b>Other Patient Experience Data Submitted in the Application</b>         |                                                                                                                              |                                               |
| <input type="checkbox"/>                                                  | Patient-focused drug development meeting summary                                                                             |                                               |
| <input type="checkbox"/>                                                  | Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel) |                                               |
| <input type="checkbox"/>                                                  | Observational survey studies                                                                                                 |                                               |
| <input type="checkbox"/>                                                  | Natural history studies                                                                                                      |                                               |
| <input type="checkbox"/>                                                  | Patient preference studies                                                                                                   |                                               |
| <input type="checkbox"/>                                                  | Other: (please specify)                                                                                                      |                                               |
| <input checked="" type="checkbox"/>                                       | If no patient experience data were submitted by Applicant, indicate here.                                                    |                                               |
| <b>Data Considered in the Assessment (But Not Submitted by Applicant)</b> |                                                                                                                              |                                               |
| <b>Check if Considered</b>                                                | <b>Type of Data</b>                                                                                                          | <b>Section Where Discussed, if Applicable</b> |
| <input type="checkbox"/>                                                  | Perspectives shared at patient stakeholder meeting                                                                           |                                               |
| <input type="checkbox"/>                                                  | Patient-focused drug development meeting summary report                                                                      |                                               |
| <input type="checkbox"/>                                                  | Other stakeholder meeting summary report                                                                                     |                                               |
| <input type="checkbox"/>                                                  | Observational survey studies                                                                                                 |                                               |
| <input type="checkbox"/>                                                  | 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.<sup>1</sup> 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.<sup>2</sup> Aleve-D Sinus and Cold is indicated for multisymptom relief of sinus pressure, headache, sinus, congestion, nasal congestion, body aches, and fever.

<sup>1</sup> Note that the pilot studies were conducted using a different formulation than the to-be-marketed formulation.

<sup>2</sup> [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).<sup>3</sup>

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

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<sup>3</sup> Refer to the Section 14 for additional information on approval basis for the listed drugs

$C_{\max}$  and  $AUC_{\text{inf}}$  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, dextrophan. However, given that dextrophan is primarily metabolized by CYP2D6 after absorption into the systemic circulation, it is reasonable that the Applicant did not measure and compare the dextrophan 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 |
|-------------------------------|--------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------|----------------------------------|-----------------------|
| <b>Pivotal clinical study</b> |                          |                                                                                                                                                                                                                                        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                             |                                  |                       |
| 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                           | <b>Test product</b> <ul style="list-style-type: none"> <li>Two ER guaifenesin 600 mg/dextromethorphan HBr 30 mg/naproxen sodium 110 mg bilayer tablets</li> </ul> <b>Reference product</b> <ul style="list-style-type: none"> <li>Co-administration of two Mucinex DM (guaifenesin 600 mg/dextromethorphan HBr 30 mg) tablets and one Aleve (naproxen sodium 220 mg) tablet</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                         | 102                         | Healthy subjects                 | Single dose           |
| <b>Pilot clinical studies</b> |                          |                                                                                                                                                                                                                                        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                             |                                  |                       |
| 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 | <b>Treatment A</b> <ul style="list-style-type: none"> <li>(b) (4) formulation ER guaifenesin 600 mg/dextromethorphan HBr 30 mg/naproxen sodium 220 mg bilayer tablet under fasted condition</li> </ul> <b>Treatment B</b> <ul style="list-style-type: none"> <li>(b) (4) formulation ER guaifenesin 600 mg/dextromethorphan HBr 30 mg/naproxen sodium 220 mg bilayer tablet under fasted condition</li> </ul> <b>Treatment C</b> <ul style="list-style-type: none"> <li>(b) (4) formulation ER guaifenesin 600 mg/dextromethorphan HBr 30 mg/naproxen sodium 220 mg bilayer tablet under fed condition</li> </ul> <b>Reference product</b> <ul style="list-style-type: none"> <li>Co-administration of Mucinex (guaifenesin) 600 mg, Vicks Formula 44 Custom Care (dextromethorphan</li> </ul> | 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 | <p><i>Treatment A</i></p> <ul style="list-style-type: none"> <li>Two capsules of (b) (4) formulation ER guaifenesin 600 mg/ dextromethorphan HBr 30 mg/naproxen sodium 110 mg bilayer tablet under fasted condition</li> </ul> <p><i>Treatment B</i></p> <ul style="list-style-type: none"> <li>Two capsules of (b) (4) formulation ER guaifenesin 600 mg/ dextromethorphan HBr 30 mg/naproxen sodium 110 mg bilayer tablet under fed condition</li> </ul> <p><i>Treatment C</i></p> <ul style="list-style-type: none"> <li>Two capsules of (b) (4) formulation ER guaifenesin 600 mg/ dextromethorphan HBr 30 mg/naproxen sodium 110 mg bilayer tablet under fasted condition</li> </ul> <p><i>Treatment D</i></p> <ul style="list-style-type: none"> <li>Two capsules of (b) (4) formulation ER guaifenesin 600 mg/ dextromethorphan HBr 30 mg/naproxen sodium 110 mg bilayer tablet under fed condition</li> </ul> <p><i>Reference product</i></p> <ul style="list-style-type: none"> <li>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</li> </ul> | 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,<sup>4</sup> 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<sub>max</sub> 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.

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<sup>4</sup> 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) <sup>1</sup> | Total MDE Upper Bound (mg) <sup>2</sup> | Supportive 21 CFR Listing | Inactive Ingredient Report Support (Y/N/NF) <sup>3</sup> |
|----------------------------|-------------|--------------------------------------------|-----------------------------------------|---------------------------|----------------------------------------------------------|
| Sodium lauryl sulfate      | 151-21-3    | (b) (4)                                    | (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

<sup>1</sup>Level of each excipient reported by the Applicant in the NDA submission, 3.2.P.1.2.1 Unit Dose Composition

<sup>2</sup>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.

<sup>3</sup>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 (49/102; 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**

| <b>TEAEs and Severity</b>           | <b>Total<br/>(N=102)</b> | <b>Treatment A<br/>(N=83)</b> | <b>Treatment B<br/>(N=82)</b> | <b>Treatment C<br/>(N=79)</b> | <b>Treatment D<br/>(N=76)</b> |
|-------------------------------------|--------------------------|-------------------------------|-------------------------------|-------------------------------|-------------------------------|
| Number of subjects reporting AE (%) | 53                       | 22<br>(26.51%)                | 14<br>(17.07%)                | 17<br>(21.52%)                | 21<br>(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**

| <b>Number of Subjects Who Discontinued (N=41)</b> | <b>Reason for Discontinuation Provided by Applicant/AE Status</b>                                                                                                                                   | <b>Case Report</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|---------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 16                                                | <ul style="list-style-type: none"> <li>COVID-19 infection</li> </ul>                                                                                                                                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| 6                                                 | <ul style="list-style-type: none"> <li>Adverse Event</li> </ul>                                                                                                                                     | <ul style="list-style-type: none"> <li><b>Subject</b> (b) (6): Discontinued for AE of fever. AE pyrexia not related to drug product. Resolved.</li> <li><b>Subject</b> (b) (6): Discontinued for AEs of high white blood cells, lymphocytes. AE not related to drug product. Resolved.</li> <li><b>Subject</b> (b) (6): Discontinued for AEs of heartburn, fatigue, dizziness, cold sweats, shortness of breath, light headedness. Resolved.</li> <li><b>Subject</b> (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.</li> <li><b>Subject</b> (b) (6): Discontinued for AE. Reported AEs stomach pain, vomit, bilateral leg pain. Resolved.</li> <li><b>Subject</b> (b) (6): Discontinued for AE. HA, moderate.</li> </ul>                                                                                                                                                                                                                         |
| 6                                                 | <ul style="list-style-type: none"> <li>Discontinued by PI per protocol for "Safety Reason" decrease in Hgb &gt;2gm/dL (compared to screening Hgb) or below 11 gm/dL</li> <li>AE reported</li> </ul> | <ul style="list-style-type: none"> <li><b>Subject</b> (b) (6): Discontinued from the study due to drop in Hgb level of 2.4 gm/dL (&gt;2 gm/dL) per protocol exclusion criteria. AE reported – "sore back."</li> <li><b>Subject</b> (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."</li> <li><b>Subject</b> (b) (6): Discontinued from the study due to Hgb level being &lt; 11gm/dL per protocol exclusion criteria. AEs reported- "HA," "foggy head," "neck stiffness."</li> <li><b>Subject</b> (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."</li> <li><b>Subject</b> (b) (6): Discontinued from the study due to Hgb level being &lt; 11gm/dL per protocol exclusion criteria. AE reported, urinary tract infection.</li> <li><b>Subject</b> (b) (6): Discontinued from the study due to Hgb level being &lt; 11gm/dL per protocol exclusion criteria. AE reported, "lightheaded."</li> </ul> |
| 2                                                 | <ul style="list-style-type: none"> <li>Personal reasons</li> <li>AE reported</li> </ul>                                                                                                             | <ul style="list-style-type: none"> <li><b>Subject</b> (b) (6): "Personal reason." AEs reported, "cold symptoms" and "HA." HA resolved without intervention.</li> <li><b>Subject</b> (b) (6): "Personal." AE reported, "HA." HA resolved without intervention.</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |

| Number of Subjects Who Discontinued (N=41) | Reason for Discontinuation Provided by Applicant/AE Status                                                                                                                                             | Case Report                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|--------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 2                                          | <ul style="list-style-type: none"> <li>Discontinued by PI per protocol for "Safety Reason" decrease in Hgb &gt;2gm/dL (compared to screening Hgb) or below 11 gm/dL</li> <li>No AE Reported</li> </ul> | <ul style="list-style-type: none"> <li><b>Subject</b> (b) (6): Discontinued from the study due to Hgb level being &lt; 11gm/dL per protocol exclusion criteria. No AE reported.</li> <li><b>Subject</b> (b) (6): Discontinued from the study due to drop in Hgb level of 2.1 gm/dL per protocol exclusion criteria. No AE reported.</li> </ul>                                                                                                                                                                                                                                                                                                                                                                  |
| 9                                          | <ul style="list-style-type: none"> <li>"Personal," "personal reason(s)," disqualified or lost to follow-up</li> <li>No AE reported</li> </ul>                                                          | <ul style="list-style-type: none"> <li><b>Subject</b> (b) (6): Lost to follow-up. No AE reported.</li> <li><b>Subject</b> (b) (6): Lost to follow-up. No AE reported.</li> <li><b>Subject</b> (b) (6): Positive drugs of abuse. No AE reported.</li> <li><b>Subject</b> (b) (6): "Personal reason." No AE reported.</li> <li><b>Subject</b> (b) (6): "Personal reason." No AE reported.</li> <li><b>Subject</b> (b) (6): "Personal." No AE reported.</li> <li><b>Subject</b> (b) (6): "Personal." No AE reported.</li> <li><b>Subject</b> (b) (6): Discontinued for "noncompliance that affects data integrity." No AE reported.</li> <li><b>Subject</b> (b) (6): COVID-19 exposure. No AE reported.</li> </ul> |

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)**

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

|         | <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/ [REDACTED] 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 [REDACTED] 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, [REDACTED], 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**

| <b>Drug-Related Treatment-Emergent Adverse Event</b> | <b>Number of Reports</b> |
|------------------------------------------------------|--------------------------|
| 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**

| <b>Preferred Term</b> | <b>All subjects<br/>(N=102)<br/>n (%)</b> | <b>Treatment A<br/>(N=83)<br/>n (%)</b> | <b>Treatment B<br/>(N=82)<br/>n (%)</b> | <b>Treatment C<br/>(N=79)<br/>n (%)</b> | <b>Treatment D<br/>(N=76)<br/>n (%)</b> |
|-----------------------|-------------------------------------------|-----------------------------------------|-----------------------------------------|-----------------------------------------|-----------------------------------------|
| 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, [REDACTED], 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 indicating 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). 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).

## 11. Advisory Committee Summary

### III. Additional Analyses and Information

## 12. Summary of Regulatory History

| Date/Activity                                                 | Outcome                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|---------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| June 5, 2009:<br>IND Opening<br>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)".<br>The study was deemed safe to proceed.                                                                                                                            |
| December 16, 2009:<br>Advice<br>Letter/Information<br>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:<br>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:<br>Type C meeting                              | A meeting was held to discuss the development plan of "(b) (4)" which RB Health proposed "(b) (4)".<br>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.<br>Regarding the Applicant's proposed indication "(b) (4)"<br>"FDA<br>(b) (4)"<br>(b) (4)                                                                                                                        |

| Date/Activity                                | Outcome                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|----------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                              | (b) (4)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| March 7, 2016:<br>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:<br>Proprietary name review | The proposed proprietary name, (b) (4), was deemed conditionally acceptable.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| June 1, 2019:<br>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:<br>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:

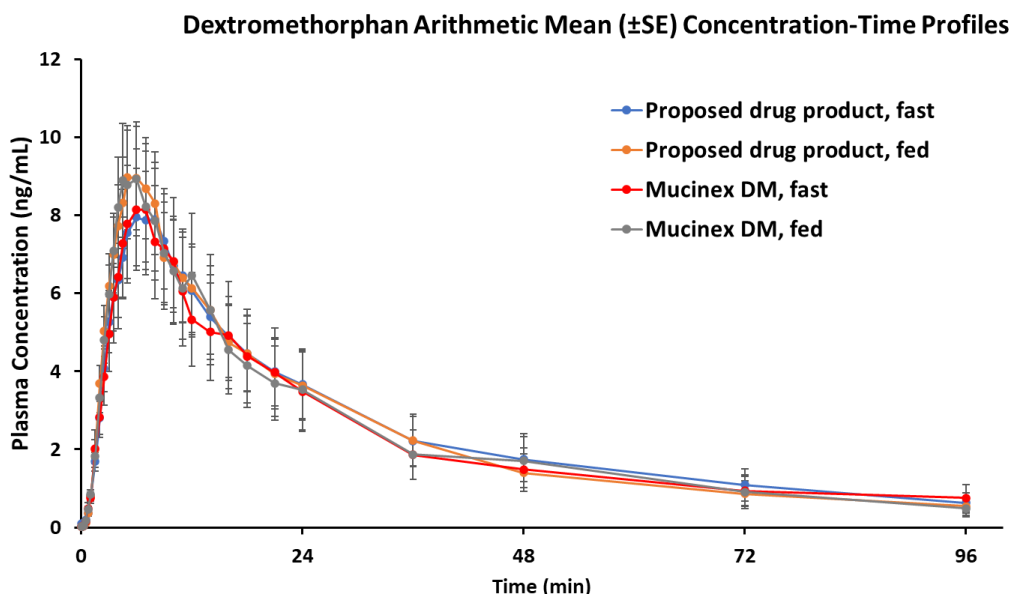
- Primary BE assessment: Treatment A (Test) versus Treatment C (Reference).
- Food effect on PK of three active ingredients following administration of proposed drug product: Treatment B versus Treatment A.
- For this food effect assessment, the reference arm was the proposed drug product under fasted 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 effect 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 ( $\pm$ 10.02) years and 76.59 ( $\pm$ 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  $\pm$  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) <sup>1</sup> (N=80) | C (Mucinex DM-Fasted Arm) (N=79) | D (Mucinex DM-Fed Arm) (N=76) |
|---------------------------------------------------------|---------------------------------------------|-------------------------------------------------------|----------------------------------|-------------------------------|
| AUC <sub>inf</sub> <sup>1</sup> (ng·h/mL)               | 272.12 $\pm$ 656.97                         | 301.77 $\pm$ 694.62                                   | 275.98 $\pm$ 750.32              | 253.27 $\pm$ 623.48           |
| AUC <sub>0-96h</sub> <sup>1</sup> (ng·h/mL)             | 235.46 $\pm$ 511.25                         | 228.48 $\pm$ 469.75                                   | 230.38 $\pm$ 568.25              | 230.60 $\pm$ 537.94           |
| C <sub>max</sub> (ng/mL)                                | 9.06 $\pm$ 12.50                            | 10.65 $\pm$ 13.58                                     | 9.60 $\pm$ 16.68                 | 10.81 $\pm$ 15.46             |
| Elimination half-life <sup>1</sup> t <sub>1/2</sub> (h) | 13.19 $\pm$ 7.90                            | 13.03 $\pm$ 8.22                                      | 13.23 $\pm$ 8.45                 | 12.34 $\pm$ 6.13              |
| T <sub>max</sub> (h) <sup>2</sup>                       | 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

<sup>1</sup> AUCs and t<sub>1/2</sub> values are not available from one subject.<sup>2</sup> Median (min, max)Abbreviations: AUC<sub>inf</sub>, area under the concentration-time curve estimated to infinity; AUC<sub>0-96h</sub>, area under the concentration-time curve from time 0 to 96 hours; C<sub>max</sub>, maximum plasma concentration; h, hour; mL, milliliter; N, number (of population); ng, nanogram; SD, standard deviation; T<sub>max</sub>, time to maximum concentration; T<sub>1/2</sub>, half-life

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

| PK Parameters                     | Listed Drug*<br>Geometric<br>LSM | Proposed Drug<br>Product** Geometric<br>LSM | Proposed/Listed Geometric Ratio<br>[Percentage (90% CI)]<br>(N=68) |
|-----------------------------------|----------------------------------|---------------------------------------------|--------------------------------------------------------------------|
| C <sub>max</sub><br>(ng/mL)       | 3.41                             | 3.24                                        | 95.31 (86.12-105.48)                                               |
| AUC <sub>0-96h</sub><br>(ng.h/mL) | 45.37                            | 46.59                                       | 102.68 (93.30-113.02)                                              |
| AUC <sub>inf</sub><br>(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 &amp; 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<sub>inf</sub>, area under the concentration-time curve estimated to infinity; AUC<sub>0-96h</sub>, area under the concentration-time curve from time 0 to 96 hours; CI, confidence interval; C<sub>max</sub>, 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<sub>max</sub> and AUC<sub>inf</sub> 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<sub>max</sub> and AUC<sub>inf</sub> 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<br>(Proposed Drug<br>Product in Fasted<br>Condition)<br>Geometric LSM | Treatment B<br>(Proposed Drug<br>Product in Fed<br>Condition)<br>Geometric LSM | Treatment B/Treatment A<br>Ratio<br>[Percentage (90% CI)] <sup>a</sup><br>(N=69) |
|--------------------------------|-----------------------------------------------------------------------------------|--------------------------------------------------------------------------------|----------------------------------------------------------------------------------|
| <i>Proposed drug product</i>   |                                                                                   |                                                                                |                                                                                  |
| C <sub>max</sub> (ng/mL)       | 3.54                                                                              | 4.76                                                                           | 134.145 (120.24-149.65)                                                          |
| AUC <sub>0-96h</sub> (ng.h/mL) | 52.20                                                                             | 64.86                                                                          | 124.24 (112.79-136.85)                                                           |
| AUC <sub>inf</sub> (ng.h/mL)   | 53.26                                                                             | 65.85                                                                          | 123.64 (112.14-136.34)                                                           |
| PK Parameters                  | Treatment C<br>(Listed Drugs -<br>Fasted Arm)<br>Geometric LSM                    | Treatment D<br>(Listed Drugs -<br>Fed Arm)<br>Geometric LSM                    | Treatment D/Treatment C<br>Ratio<br>[Percentage (90% CI)] <sup>b</sup><br>(N=66) |
| <i>Listed drug</i>             |                                                                                   |                                                                                |                                                                                  |
| C <sub>max</sub> (ng/mL)       | 3.16                                                                              | 4.52                                                                           | 142.59 (126.21-161.09)                                                           |
| AUC <sub>0-96h</sub> (ng.h/mL) | 42.11                                                                             | 51.40                                                                          | 122.04 (109.11-136.51)                                                           |
| AUC <sub>inf</sub> (ng.h/mL)   | 42.87                                                                             | 52.21                                                                          | 121.76 (108.83-136.24)                                                           |

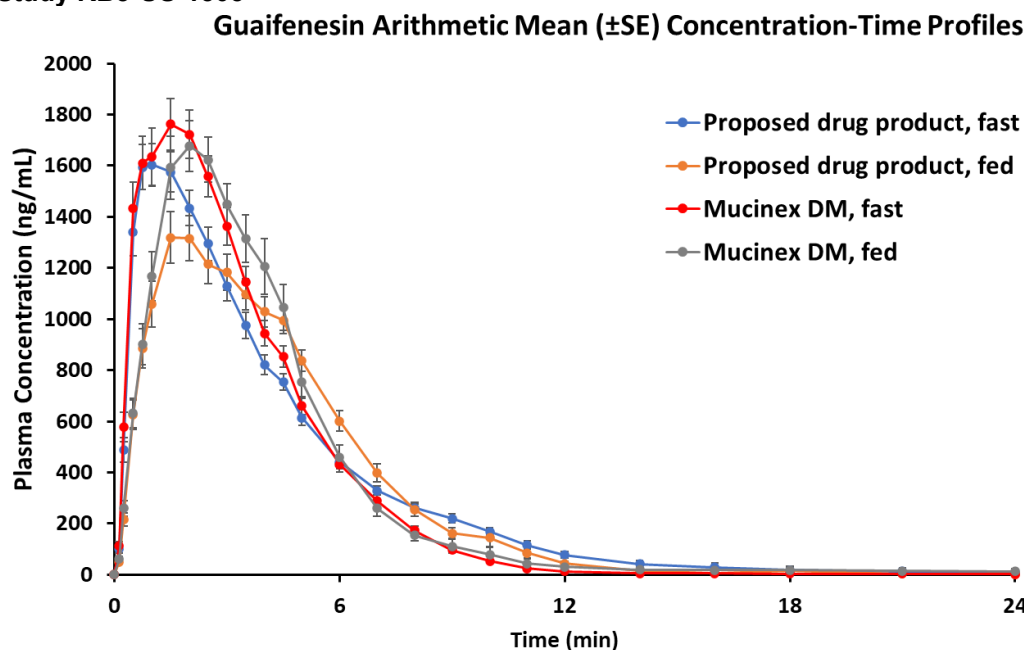
Source: FDA Analysis using ADPC.xpt from Study RB5-US-1505

<sup>a</sup> 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)<sup>b</sup> For this food effect 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<sub>inf</sub>, area under the concentration-time curve estimated to infinity; AUC<sub>0-96h</sub>, area under the concentration-time curve from time 0 to 96 hours; CI, confidence interval; C<sub>max</sub>, 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  $\pm$  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 <sub>inf</sub> (ng·h/mL)                | 8058.90 $\pm$ 3240.55                       | 7532.11 $\pm$ 2864.55                      | 8001.80 $\pm$ 2949.30              | 8171.63 $\pm$ 4495.06         |
| AUC <sub>0-24h</sub> (ng·h/mL)              | 8026.11 $\pm$ 3242.85                       | 7489.15 $\pm$ 2866.35                      | 7966.80 $\pm$ 2950.73              | 8128.63 $\pm$ 4498.91         |
| C <sub>max</sub> (ng/mL)                    | 1870.54 $\pm$ 792.68                        | 1671.38 $\pm$ 936.96                       | 2145.99 $\pm$ 1053.45              | 2174.36 $\pm$ 1093.44         |
| Elimination half-life, t <sub>1/2</sub> (h) | 8.96 $\pm$ 2.06                             | 11.07 $\pm$ 3.19                           | 9.70 $\pm$ 1.47                    | 11.92 $\pm$ 2.49              |
| T <sub>max</sub> (h) <sup>1</sup>           | 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

<sup>1</sup> Median (min- max)

Abbreviations: AUC<sub>inf</sub>, area under the concentration-time curve estimated to infinity; AUC<sub>0-24h</sub>, area under the concentration-time curve from time 0 to 24 hours; C<sub>max</sub>, maximum plasma concentration; h, hour; mL, milliliter; N, number (of population); ng, nanogram; PK, pharmacokinetic; SD, standard deviation; T<sub>max</sub>, time to maximum concentration; T<sub>1/2</sub>, half-life

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

| PK Parameters                  | Listed Drug*<br>Geometric LSM | Proposed Drug Product**<br>Geometric LSM | Proposed/Listed Geometric Ratio<br>[Percentage (90% CI)]<br>(N=68) |
|--------------------------------|-------------------------------|------------------------------------------|--------------------------------------------------------------------|
| C <sub>max</sub> (ng/mL)       | 1966.82                       | 1774.75                                  | 90.23 (85.46-95.26)                                                |
| AUC <sub>0-24h</sub> (ng.h/mL) | 7384.41                       | 7320.21                                  | 99.13 (95.35-103.05)                                               |
| AUC <sub>inf</sub> (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 &amp; 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<sub>inf</sub>, area under the concentration-time curve estimated to infinity; AUC<sub>0-24h</sub>, area under the concentration-time curve from time 0 to 24 hours; CI, confidence interval; C<sub>max</sub>, 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<sub>max</sub> and AUC<sub>inf</sub> 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<sub>max</sub> 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**

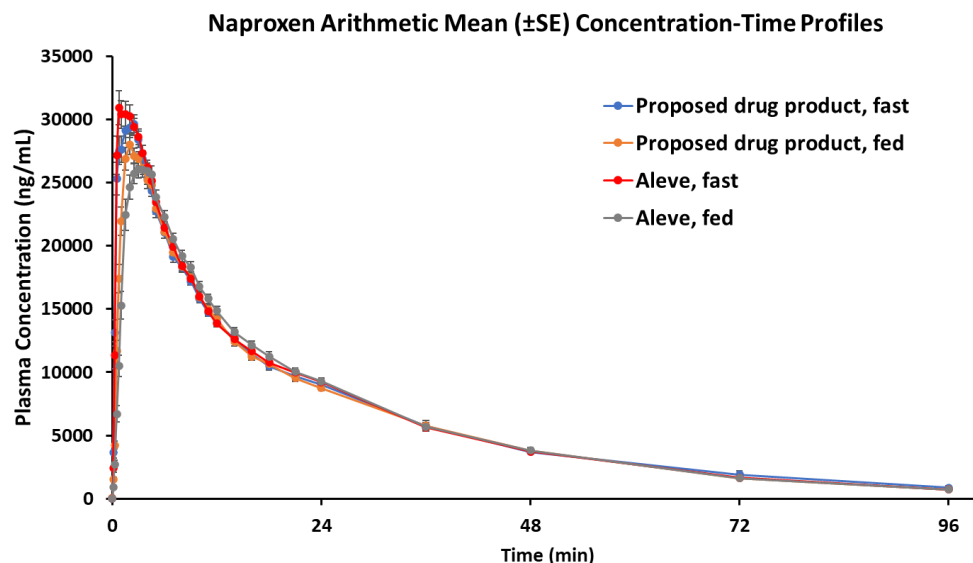
| PK Parameters                    | Treatment A<br>(Proposed Drug Product in Fasted Condition) <sup>a</sup><br>Geometric LSM | Treatment B<br>(Proposed Drug Product in Fed Condition) <sup>b</sup><br>Geometric LSM | Fed/Fasted Ratio<br>[Percentage (90% CI)]<br>(N=70) |
|----------------------------------|----------------------------------------------------------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

Source: FDA Analysis using ADPC.xpt from Study RB5-US-1505

<sup>a</sup> The reference arm is the proposed drug product under fasted condition (Treatment A: two Mucinex 12 HR Cold & Fever tablets after 10-hour fast)<sup>b</sup> 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<sub>inf</sub>, area under the concentration-time curve estimated to infinity; AUC<sub>0-24h</sub>, area under the concentration-time curve from time 0 to 24 hours; CI, confidence interval; C<sub>max</sub>, 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  $\pm$  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 <sub>inf</sub> (ng.h/mL)               | 662784.36<br>$\pm$ 218514.68                  | 624415.18<br>$\pm$ 154348.34               | 652111.70<br>$\pm$ 136980.90         | 637862.51<br>$\pm$ 136345.08      |
| AUC <sub>0-96h</sub> (ng.h/mL)             | 622895.71<br>$\pm$ 152604.37                  | 598130.92<br>$\pm$ 150952.01               | 627560.21<br>$\pm$ 129751.97         | 612217.64<br>$\pm$ 129153.92      |
| C <sub>max</sub> (ng/mL)                   | 36302.41<br>$\pm$ 7866.14                     | 32623.46<br>$\pm$ 6432.58                  | 38202.53<br>$\pm$ 8352.67            | 31192.11<br>$\pm$ 6637.32         |
| Elimination half-life t <sub>1/2</sub> (h) | 20.43<br>$\pm$ 5.39                           | 19.30<br>$\pm$ 3.85                        | 19.83<br>$\pm$ 3.54                  | 19.51<br>$\pm$ 3.65               |
| T <sub>max</sub> (h)                       | 1.5<br>(0.5-18)                               | 2<br>(0.75-36)                             | 1<br>(0.5-7)                         | 3<br>(0.75-18)                    |

Source: FDA Analysis using ADPC.xpt from Study RB5-US-1505

Abbreviations: AUC<sub>inf</sub>, area under the concentration-time curve estimated to infinity; AUC<sub>0-96h</sub>, area under the concentration-time curve from time 0 to 96 hours; C<sub>max</sub>, maximum plasma concentration; h, hour; mL, milliliter; N, number (of population); ng, nanogram; PK, pharmacokinetic; SD, standard deviation; t<sub>1/2</sub>, half-life

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

| PK Parameters                  | Listed Drug*<br>Geometric LSM | Proposed Drug Product**<br>Geometric LSM | Proposed/Listed Geometric Ratio [Percentage (90% CI)]<br>(N=68) |
|--------------------------------|-------------------------------|------------------------------------------|-----------------------------------------------------------------|
| C <sub>max</sub> (ng/mL)       | 37976.34                      | 36541.93                                 | 96.22 (92.43-100.17)                                            |
| AUC <sub>0-96h</sub> (ng.h/mL) | 631689.28                     | 634631.18                                | 100.46 (97.50-103.52)                                           |
| AUC <sub>inf</sub> (ng.h/mL)   | 656452.96                     | 667355.92                                | 101.66 (97.80- 105.66)                                          |
| AUC <sub>0-12h</sub> (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 &amp; 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<sub>inf</sub>, area under the concentration-time curve estimated to infinity; AUC<sub>0-12h</sub>, area under the concentration-time curve from time 0 to 12 hours; AUC<sub>0-96h</sub>, area under the concentration-time curve from time 0 to 96 hours; CI, confidence interval; C<sub>max</sub>, 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<sub>max</sub> and AUC<sub>inf</sub> 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<sub>max</sub> 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<br>(Proposed Drug Product in Fasted Condition) <sup>a</sup><br>Geometric LSM | Treatment B<br>(Proposed Drug Product in Fed Condition) <sup>b</sup><br>Geometric LSM | Fed/Fasted Ratio<br>[Percentage (90% CI)]<br>(N=70) |
|--------------------------------|------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|-----------------------------------------------------|
| C <sub>max</sub> (ng/mL)       | 36166.176                                                                                | 32635.701                                                                             | 90.23 (86.18-94.48)                                 |
| AUC <sub>0-96h</sub> (ng.h/mL) | 624718.74                                                                                | 606639.19                                                                             | 97.11 (93.38-100.98)                                |
| AUC <sub>inf</sub> (ng.h/mL)   | 653365.3                                                                                 | 629009.61                                                                             | 96.27 (91.95-100.78)                                |

Source: FDA Analysis using ADPC.xpt from Study RB5-US-1505

<sup>a</sup> 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).<sup>b</sup> 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<sub>inf</sub>, area under the concentration-time curve estimated to infinity; AUC<sub>0-96h</sub>, area under the concentration-time curve from time 0 to 96 hours; C<sub>max</sub>, 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<sub>2</sub>EDTA human plasma. It was developed and validated with study protocol (b) (4) Study Number: 1375-1902.<sup>5,6,7</sup> 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                                             | <b>Dextromethorphan</b>                                                                                                 | <b>Guaifenesin</b>                              | <b>Naproxen</b>                                         |
| Internal Standard                                        | Dextromethorphan-d3                                                                                                     | Guaifenesin-d3                                  | Naproxen-d3                                             |
| 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                                             |

<sup>5</sup> [\\CDSESUB1\EVSPROD\nda217338\0003\m5\53-clin-stud-rep\531-rep-biopharm-stud\5314-bioanalyt-analyt-met\1375-1902\1375-1902.pdf](#)

<sup>6</sup> [\\CDSESUB1\EVSPROD\nda217338\0003\m5\53-clin-stud-rep\531-rep-biopharm-stud\5314-bioanalyt-analyt-met\1375-1902\1375-1902-amend-1.pdf](#)

<sup>7</sup> [\\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:<br>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<br>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)<br>Accuracy: RE% (-9.9)                                                                                                                                                                                                                                                                                                                                            | Precision: CV% (2.4)<br>Accuracy: RE% (-10.4)                             | Precision: CV% (10.7)<br>Accuracy: RE% (-4.8)                       |
| 2% Hemolyzed Plasma Test <sup>8</sup>         | No impact on assay performance                                                                                                                                                                                                                                                                                                                                                          |                                                                           |                                                                     |
| Lipemic Plasma Test <sup>9</sup>              | No impact on assay performance                                                                                                                                                                                                                                                                                                                                                          |                                                                           |                                                                     |
| Batch Size Test                               | 159 Injections                                                                                                                                                                                                                                                                                                                                                                          |                                                                           |                                                                     |
| Carryover <sup>10</sup>                       | <20% LLOQ (Dextromethorphan)<br><5% Carryover IS (Dextromethorphan-d <sub>3</sub> )                                                                                                                                                                                                                                                                                                     | <20% LLOQ (Guaifenesin)<br><5% Carryover IS (Guaifenesin-d <sub>3</sub> ) | <20% LLOQ (Naproxen)<br><5% Carryover IS (Naproxen-d <sub>3</sub> ) |

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

<sup>8</sup> [NDA 217338; Bioanalytical method validation report; \(Protocol # 1375-1902\)](#); Table 21-23

<sup>9</sup> [NDA 217338; Bioanalytical method validation report; \(Protocol # 1375-1902\)](#); Table 26-28

<sup>10</sup> [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               | <ul style="list-style-type: none"> <li><i>Dextromethorphan</i>: 97 of 103 runs (94.2%) met acceptance criteria, including ISR runs. Three runs were rejected, and three runs were aborted.</li> <li><i>Guaifenesin</i>: 85 of 88 runs (96.6%) met acceptance criteria, including incurred sample reanalysis. One run was rejected, and two runs were aborted.</li> <li><i>Naproxen</i>: 82 of 84 runs (97.6%) met acceptance criteria, including ISR runs. No runs were rejected, and two runs were aborted.</li> </ul> |
| Standard Calibration Curve       | <ul style="list-style-type: none"> <li><i>Dextromethorphan</i>: 8 calibration standards from 0.01 to 10 ng/mL</li> <li><i>Guaifenesin</i>: 8 calibration standards from 5 to 5000 ng/mL</li> <li><i>Naproxen</i>: 8 calibration standards from 50 to 50000 ng/mL</li> </ul>                                                                                                                                                                                                                                             |
| Standard Calibration Performance | <ul style="list-style-type: none"> <li><i>Dextromethorphan</i>: Cumulative bias range: -2.3% to 3.0%</li> <li><i>Guaifenesin</i>: Cumulative bias range: -2.2% to 2.2%</li> <li><i>Naproxen</i>: Cumulative bias range: -2.7% to 2.6%</li> <li><i>Dextromethorphan</i>: Cumulative precision: □5.9% CV</li> <li><i>Guaifenesin</i>: Cumulative precision: □6.6% CV</li> <li><i>Naproxen</i>: Cumulative precision: □5.0% CV</li> </ul>                                                                                  |
| QC Performance                   | <ul style="list-style-type: none"> <li><i>Dextromethorphan</i>: Cumulative bias range: -0.5% to 3.3%</li> <li><i>Guaifenesin</i>: Cumulative bias range: -0.8% to 3.0%</li> <li><i>Naproxen</i>: Cumulative bias range: -0.8% to 3.5%</li> <li><i>Dextromethorphan</i>: Cumulative precision: □6.8% CV</li> <li><i>Guaifenesin</i>: Cumulative precision: □6.9% CV</li> <li><i>Naproxen</i>: Cumulative precision: □6.6% CV</li> </ul>                                                                                  |
| Method Reproducibility           | <ul style="list-style-type: none"> <li><i>Dextromethorphan</i>: ISR was performed in 530 (5.6%) of 9522 analyzed study samples, and 80.9% met the pre-specified acceptance criteria.</li> <li><i>Guaifenesin</i>: ISR was performed in 536 (5.6%) of 9522 analyzed study samples, and 93.1% met the pre-specified acceptance criteria.</li> <li><i>Naproxen</i>: ISR was performed in 550 (5.8%) of 9522 analyzed study samples, and 93.3% met the pre-specified acceptance criteria.</li> </ul>                        |
| 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<sup>11</sup>

Abbreviations: C, Celsius; CV, coefficient of variation; ISR, incurred sample reanalysis; LC-MS/MS, liquid chromatography with tandem mass spectrometry; QC, quality check

<sup>11</sup> [\\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)

## **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 <sup>®</sup> , 220 mg naproxen sodium (200 mg naproxen), and 60 mg dextromethorphan - Test A (fasted)                                                                          |           |         |        |        |         |
| Treatment B (Test B fasted) = 1 x 600 mg Mucinex <sup>®</sup> , 220 mg naproxen sodium (200 mg naproxen), and 60 mg dextromethorphan - Test B (fasted)                                                                          |           |         |        |        |         |
| Treatment C (Test A fed) = 1 x 600 mg Mucinex <sup>®</sup> , 220 mg naproxen sodium (200 mg naproxen), and 60 mg dextromethorphan - Test A (fed)                                                                                |           |         |        |        |         |
| Treatment D (Reference fasted) = 1 x 600 mg Mucinex <sup>®</sup> , 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**

| SOC                                             | PT                            | Treatment A |        | Treatment B |        | Treatment C |        | Treatment D |        | Treatment E |        |
|-------------------------------------------------|-------------------------------|-------------|--------|-------------|--------|-------------|--------|-------------|--------|-------------|--------|
|                                                 |                               | 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 Hyperemia              | 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 Disorders | Muscle Spasms                 | 0           | 0      | 1           | 1      | 0           | 0      | 0           | 0      | 0           | 0      |
|                                                 | Pain in Extremity             | 0           | 0      | 0           | 0      | 0           | 0      | 0           | 0      | 1           | 1      |
| Nervous System Disorders                        |                               |             |        |             |        |             |        |             |        |             |        |
| Skin and Subcutaneous Tissue Disorders          | Headache                      | 1           | 1      | 1           | 1      | 0           | 0      | 0           | 0      | 0           | 0      |
|                                                 | 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

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)  
(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**



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 <input checked="" type="checkbox"/> <input type="checkbox"/> | No <input type="checkbox"/> (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                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                                                  |                                                                  |
| <p>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)):</p> <p>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: Not applicable</p> <p>Significant payments of other sorts: Not applicable</p> <p>Proprietary interest in the product tested held by investigator: Not applicable</p> <p>Significant equity interest held by investigator: Not applicable</p> <p>Sponsor of covered study: Not applicable</p> |                                                                  |                                                                  |
| Is an attachment provided with details of the disclosable financial interests/arrangements:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | Yes <input type="checkbox"/>                                     | No <input type="checkbox"/> (Request details from Applicant)     |
| Is a description of the steps taken to minimize potential bias provided:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | Yes <input type="checkbox"/>                                     | No <input type="checkbox"/> (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 <input type="checkbox"/>                                     | No <input type="checkbox"/> (Request explanation from Applicant) |

Abbreviation: FDA, Food and Drug Administration

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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                | Dorothy Chang           |
| DNPD I Clinical Team Leader                   |                         |
| 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 Hearn-Stewart, Nikia Morris                                                                                |
| Medical Editors      | Monika Deshpande, Allison Cruz                                                                                    |

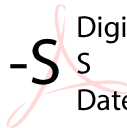
Abbreviations: DAAP, Division of Anesthesiology, Addiction Medicine, and Pain Medicine; DEPI, Division of Epidemiology; DMEPA, Division of Medication Error Prevention and Analysis; DRISK, Division of Risk Management; IAMA, Integrated Assessment of Marketing Applications; OND, Office of New Drugs; OPDP, 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<br>Regulatory Project Manager                                                                                                                                                                                                                  | Tam Dinh<br>OND/ORO/DR O-NPD               | <input type="checkbox"/> Benefit-Risk Assessment<br><input type="checkbox"/> Interdisciplinary Assessment<br><input checked="" type="checkbox"/> Additional Information and Analyses<br>Sections: <a href="#">12</a>                          | Based on my assessment of the application:<br><input type="checkbox"/> <u>No</u> deficiencies preclude approval.<br><input checked="" type="checkbox"/> Deficiencies preclude approval.<br><input type="checkbox"/> Not applicable. |                                         | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No |
| Signature/date/time stamp: <div style="text-align: right;">             Digitally signed by Tam Dinh -S<br/>             Date: 2024.07.24 09:25:32 -04'00'           </div> <div style="text-align: center; font-size: 2em;">             Tam Dinh -S           </div>       |                                            |                                                                                                                                                                                                                                               |                                                                                                                                                                                                                                     |                                         |                                                                        |
| Regulatory Project Management<br>CPMS                                                                                                                                                                                                                                        | Daniel Brum<br>OND/ORO/DR O-NPD            | <input type="checkbox"/> Benefit-Risk Assessment<br><input type="checkbox"/> Interdisciplinary Assessment<br><input type="checkbox"/> Additional Information and Analyses<br>Sections: N/A (Suggested edits for clarity to multiple sections) | Based on my assessment of the application:<br><input type="checkbox"/> No deficiencies preclude approval.<br><input checked="" type="checkbox"/> Deficiencies preclude approval.<br><input type="checkbox"/> Not applicable.        |                                         | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No |
| Signature/date/time stamp: <div style="text-align: right;">             Digitally signed by Daniel Brum -S<br/>             Date: 2024.07.26 13:21:26 -04'00'           </div> <div style="text-align: center; font-size: 2em;">             Daniel Brum -S           </div> |                                            |                                                                                                                                                                                                                                               |                                                                                                                                                                                                                                     |                                         |                                                                        |

| 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<br>Secondary Reviewer                                                                                                                                                                                                                                      | Yunzhao Ren<br>OTS/OCP/DII P               | <input type="checkbox"/> Benefit-Risk Assessment<br><input type="checkbox"/> Interdisciplinary Assessment<br><input type="checkbox"/> Additional Information and Analyses<br>Sections: <a href="#">5,6,3,10,14</a> | Based on my assessment of the application:<br><input type="checkbox"/> <u>No</u> deficiencies preclude approval.<br><input checked="" type="checkbox"/> Deficiencies preclude approval.<br><input type="checkbox"/> Not applicable. |                                         | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No |
| Signature/date/time stamp: <div style="text-align: center;">  <p><b>Yunzhao Ren -S</b></p> <p>Digitally signed by Yunzhao Ren -S<br/>Date: 2024.07.23 16:33:52 -04'00'</p> </div>              |                                            |                                                                                                                                                                                                                    |                                                                                                                                                                                                                                     |                                         |                                                                        |
| Clinical Pharmacology<br>Reviewer                                                                                                                                                                                                                                                | Sanjida Mahjabeen<br>OTS/OCP/DII P         | <input type="checkbox"/> Benefit-Risk Assessment<br><input type="checkbox"/> Interdisciplinary Assessment<br><input type="checkbox"/> Additional Information and Analyses<br>Sections: <a href="#">5,6,3,10,14</a> | Based on my assessment of the application:<br><input type="checkbox"/> <u>No</u> deficiencies preclude approval.<br><input checked="" type="checkbox"/> Deficiencies preclude approval.<br><input type="checkbox"/> Not applicable. |                                         | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No |
| Signature/date/time stamp: <div style="text-align: center;">  <p><b>Sanjida Mahjabeen -S</b></p> <p>Digitally signed by Sanjida Mahjabeen -S<br/>Date: 2024.07.23 16:29:19 -04'00'</p> </div> |                                            |                                                                                                                                                                                                                    |                                                                                                                                                                                                                                     |                                         |                                                                        |

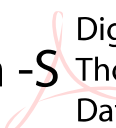
| Discipline and Role                                                                                                                         | Reviewer Name, Office/Center, and Division | Sections Authored in Full or in Part                                                                           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

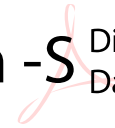
| Discipline and Role                                                                                                                                                                                                                                                                    | Reviewer Name, Office/Center, 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<br>OND/ONPD/D<br>NPDI        | <input checked="" type="checkbox"/> Benefit-Risk Assessment<br><input checked="" type="checkbox"/> Interdisciplinary Assessment<br><input checked="" type="checkbox"/> Additional Information and Analyses<br>Sections:                                                                  | Based on my assessment of the application:<br><input type="checkbox"/> <u>No</u> deficiencies preclude approval.<br><input checked="" type="checkbox"/> Deficiencies preclude approval.<br><input type="checkbox"/> Not applicable. |                                         | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No |
| Signature/date/time stamp:<br><div style="text-align: center;">  <b>Dorothy Chang -S</b> Digitally signed by Dorothy Chang -S<br/>             Date: 2024.07.26 13:25:39 -04'00'           </div>     |                                            |                                                                                                                                                                                                                                                                                          |                                                                                                                                                                                                                                     |                                         |                                                                        |
| Clinical Reviewer                                                                                                                                                                                                                                                                      | Aklil Getachew<br>OND/ONPD/D<br>NPDI       | <input checked="" type="checkbox"/> Benefit-Risk Assessment<br><input checked="" type="checkbox"/> Interdisciplinary Assessment<br><input checked="" type="checkbox"/> Additional Information and Analyses<br>Sections:<br><a href="#">1,2,3,6.2,6.3,7.2,7.3,7.4,7.5,7.6,7.7,8,12,17</a> | Based on my assessment of the application:<br><input type="checkbox"/> <u>No</u> deficiencies preclude approval.<br><input checked="" type="checkbox"/> Deficiencies preclude approval.<br><input type="checkbox"/> Not applicable. |                                         | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No |
| Signature/date/time stamp:<br><div style="text-align: center;">  <b>Aklil Getachew -S</b> Digitally signed by Aklil Getachew -S<br/>             Date: 2024.07.26 09:18:35 -04'00'           </div> |                                            |                                                                                                                                                                                                                                                                                          |                                                                                                                                                                                                                                     |                                         |                                                                        |

| 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<br>OND/ON/DAA<br>P         | <input type="checkbox"/> Benefit-Risk Assessment<br><input checked="" type="checkbox"/> Interdisciplinary Assessment<br><input type="checkbox"/> Additional Information and Analyses<br>Sections:<br><a href="#">6.3.1</a> | Based on my assessment of the application:<br><br><input type="checkbox"/> <u>No</u> deficiencies preclude approval.<br><input checked="" type="checkbox"/> Deficiencies preclude approval.<br><input type="checkbox"/> Not applicable. |                                         | <input checked="" type="checkbox"/> Yes<br><br><input type="checkbox"/> No |
| Signature/date/time stamp:<br><br><div> <div>Nancy C. Dickinson -S</div> <div>Digitally signed by Nancy C. Dickinson -S<br/>Date: 2024.07.25 09:35:55 -04'00'</div> </div> |                                            |                                                                                                                                                                                                                            |                                                                                                                                                                                                                                         |                                         |                                                                            |
| Clinical Reviewer                                                                                                                                                          | Timothy Jiang<br>OND/ON/DAA<br>P           | <input type="checkbox"/> Benefit-Risk Assessment<br><input checked="" type="checkbox"/> Interdisciplinary Assessment<br><input type="checkbox"/> Additional Information and Analyses<br>Sections:<br><a href="#">6.3.1</a> | Based on my assessment of the application:<br><br><input type="checkbox"/> No deficiencies preclude approval.<br><input checked="" type="checkbox"/> Deficiencies preclude approval.<br><input type="checkbox"/> Not applicable.        |                                         | <input checked="" type="checkbox"/> Yes<br><br><input type="checkbox"/> No |
| Signature/date/time stamp:<br><br><div> <div>Timothy Jiang -S</div> <div>Digitally signed by Timothy Jiang -S<br/>Date: 2024.07.25 08:47:34 -04'00'</div> </div>           |                                            |                                                                                                                                                                                                                            |                                                                                                                                                                                                                                         |                                         |                                                                            |

| 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<br>Team Leader                                                                                                                                                                            | Steven Adah<br>OND/ONPD/D<br>NPDI          | <input type="checkbox"/> Benefit-Risk Assessment<br><input type="checkbox"/> Interdisciplinary Assessment<br><input checked="" type="checkbox"/> Additional Information and Analyses<br>Sections: <a href="#">23</a> | Based on my assessment of the application:<br><input type="checkbox"/> <u>No</u> deficiencies preclude approval.<br><input checked="" type="checkbox"/> Deficiencies preclude approval.<br><input type="checkbox"/> Not applicable. |                                         | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No |
| Signature/date/time stamp: Michelle Walker signing on behalf of Steven Adah<br><br><div> <div>Michelle Walker -S</div> <div>Digitally signed by Michelle Walker -S<br/>Date: 2024.07.24 12:02:24 -04'00'</div> </div> |                                            |                                                                                                                                                                                                                      |                                                                                                                                                                                                                                     |                                         |                                                                        |
| Interdisciplinary Scientist<br>Reviewer                                                                                                                                                                               | Michelle Walker<br>OND/ONPD/D<br>NPDI      | <input type="checkbox"/> Benefit-Risk Assessment<br><input type="checkbox"/> Interdisciplinary Assessment<br><input checked="" type="checkbox"/> Additional Information and Analyses<br>Sections: <a href="#">23</a> | Based on my assessment of the application:<br><input type="checkbox"/> <u>No</u> deficiencies preclude approval.<br><input checked="" type="checkbox"/> Deficiencies preclude approval.<br><input type="checkbox"/> Not applicable. |                                         | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No |
| Signature/date/time stamp:<br><br><div> <div>Michelle Walker -S</div> <div>Digitally signed by Michelle Walker -S<br/>Date: 2024.07.24 12:01:44 -04'00'</div> </div>                                                  |                                            |                                                                                                                                                                                                                      |                                                                                                                                                                                                                                     |                                         |                                                                        |

| 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<br>OPQOPQAI/IX         | <input type="checkbox"/> Benefit-Risk Assessment<br><input type="checkbox"/> Interdisciplinary Assessment<br><input type="checkbox"/> Additional Information and Analyses<br>Sections: <a href="#">9</a>            | Based on my assessment of the application:<br><input checked="" type="checkbox"/> <u>No</u> deficiencies preclude approval.<br><input type="checkbox"/> Deficiencies preclude approval.<br><input type="checkbox"/> Not applicable. |                                         | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No |
| Signature/date/time stamp:<br><div style="display: flex; justify-content: space-between; align-items: center;"> <div style="text-align: center;"> <b>Danae D. Christodoulou -S</b> </div> <div style="text-align: right;">           Digitally signed by Danae D. Christodoulou -S<br/>           Date: 2024.07.25 14:07:24 -04'00'         </div> </div> |                                            |                                                                                                                                                                                                                     |                                                                                                                                                                                                                                     |                                         |                                                                        |
| Product Quality Senior Pharmaceutical Quality Assessor, Application Team Lead                                                                                                                                                                                                                                                                             | Swapan De<br>OPQOPQAI/IX                   | <input checked="" type="checkbox"/> Benefit-Risk Assessment<br><input type="checkbox"/> Interdisciplinary Assessment<br><input type="checkbox"/> Additional Information and Analyses<br>Sections: <a href="#">9</a> | Based on my assessment of the application:<br><input checked="" type="checkbox"/> <u>No</u> deficiencies preclude approval.<br><input type="checkbox"/> Deficiencies preclude approval.<br><input type="checkbox"/> Not applicable. |                                         | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No |
| Signature/date/time stamp:<br><div style="display: flex; justify-content: space-between; align-items: center;"> <div style="text-align: center;"> <b>Swapan K. De -S</b> </div> <div style="text-align: right;">           Digitally signed by Swapan K. De -S<br/>           Date: 2024.07.25 09:25:56 -04'00'         </div> </div>                     |                                            |                                                                                                                                                                                                                     |                                                                                                                                                                                                                                     |                                         |                                                                        |

| 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<br>Team Leader                                                                                                                                                                                                                                      | Donald Charles Thompson<br>OND/ONDP/NPDPTS | <input type="checkbox"/> Benefit-Risk Assessment<br><input type="checkbox"/> Interdisciplinary Assessment<br><input type="checkbox"/> Additional Information and Analyses<br>Sections <a href="#">7.1</a> | Based on my assessment of the application:<br><input checked="" type="checkbox"/> <u>No</u> deficiencies preclude approval.<br><input type="checkbox"/> Deficiencies preclude approval.<br><input type="checkbox"/> Not applicable. |                                         | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No |
| Signature/date/time stamp:<br><div style="text-align: center;">              Digitally signed by D Charles Thompson -S<br/>             Date: 2024.07.26 11:59:08 -04'00'           </div> |                                            |                                                                                                                                                                                                           |                                                                                                                                                                                                                                     |                                         |                                                                        |

| 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<br>Reviewer                                                                                                                                                                                                                                         | Chibueze Ihunnah<br>OND/ONDP/NPDPTS        | <input type="checkbox"/> Benefit-Risk Assessment<br><input type="checkbox"/> Interdisciplinary Assessment<br><input type="checkbox"/> Additional Information and Analyses<br>Sections: <a href="#">7.1</a> | Based on my assessment of the application:<br><input checked="" type="checkbox"/> <u>No</u> deficiencies preclude approval.<br><input type="checkbox"/> Deficiencies preclude approval.<br><input type="checkbox"/> Not applicable. |                                         | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No |
| Signature/date/time stamp:<br><div style="text-align: center;">              Digitally signed by Chibueze Ihunnah -S<br/>             Date: 2024.07.26 11:53:48 -04'00'           </div> |                                            |                                                                                                                                                                                                            |                                                                                                                                                                                                                                     |                                         |                                                                        |

| 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<br>OCD/CSS                    | <input type="checkbox"/> Benefit-Risk Assessment<br><input type="checkbox"/> Interdisciplinary Assessment<br><input type="checkbox"/> Additional Information and Analyses<br>Sections: <a href="#">7.7.3</a>                                                     | Based on my assessment of the application:<br><input checked="" type="checkbox"/> No deficiencies preclude approval.<br><input type="checkbox"/> Deficiencies preclude approval.<br><input type="checkbox"/> Not applicable.        | CSS reviewed this application from an abuse potential perspective. The application assessment of "No deficiencies preclude approval" applies <i>only</i> to abuse potential. | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No |
| Signature/date/time stamp:<br><div> <div>Chad Reissig -S</div> <div>Digitally signed by Chad Reissig -S<br/>Date: 2024.07.25 11:14:30 -04'00'</div> </div>                                                                     |                                            |                                                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                     |                                                                                                                                                                              |                                                                        |
| Clinical Pharmacology Team Leader                                                                                                                                                                                              | Yuching Yang<br>OTS/OCP/DP M               | <input type="checkbox"/> Benefit-Risk Assessment<br><input type="checkbox"/> Interdisciplinary Assessment<br><input checked="" type="checkbox"/> Additional Information and Analyses<br>Sections: <a href="#">5</a> , <a href="#">6.3</a> , <a href="#">14.5</a> | Based on my assessment of the application:<br><input type="checkbox"/> <u>No</u> deficiencies preclude approval.<br><input checked="" type="checkbox"/> Deficiencies preclude approval.<br><input type="checkbox"/> Not applicable. |                                                                                                                                                                              | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No |
| Signature/date/time stamp: Manuela Grimstein signing on behalf of Yuching Yang<br><div> <div>Manuela D. Grimstein -S</div> <div>Digitally signed by Manuela D. Grimstein -S<br/>Date: 2024.07.25 14:50:41 -04'00'</div> </div> |                                            |                                                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                     |                                                                                                                                                                              |                                                                        |

| 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<br>Reviewer                                                                                                                                                                                                                                                           | Manuela Grimstein<br>OTS/OCP/DP M          | <input type="checkbox"/> Benefit-Risk Assessment<br><input type="checkbox"/> Interdisciplinary Assessment<br><input checked="" type="checkbox"/> Additional Information and Analyses<br>Sections: <a href="#">5</a> , <a href="#">6.3</a> , <a href="#">14.5</a> | Based on my assessment of the application:<br><input type="checkbox"/> <u>No</u> deficiencies preclude approval.<br><input checked="" type="checkbox"/> Deficiencies preclude approval.<br><input type="checkbox"/> Not applicable. |                                         | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No |
| Signature/date/time stamp:<br><div> <div>Manuela D. Grimstein -S</div> <div>            Digitally signed by Manuela D. Grimstein -S<br/>           Date: 2024.07.25 14:50:04 -04'00'         </div> </div> |                                            |                                                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                     |                                         |                                                                        |
| Clinical Signatory Authority                                                                                                                                                                                                                                                                | Nushin Todd<br>OND/ONPD/D NPDI             | <input checked="" type="checkbox"/> Benefit-Risk Assessment<br><input checked="" type="checkbox"/> Interdisciplinary Assessment<br><input checked="" type="checkbox"/> Additional Information and Analyses<br>Sections:                                          | Based on my assessment of the application:<br><input type="checkbox"/> <u>No</u> deficiencies preclude approval.<br><input checked="" type="checkbox"/> Deficiencies preclude approval.<br><input type="checkbox"/> Not applicable. |                                         | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No |
| Signature/date/time stamp:<br><div> <div>Nushin Todd -S</div> <div>            Digitally signed by Nushin Todd -S<br/>           Date: 2024.07.26 14:26:01 -04'00'         </div> </div>                 |                                            |                                                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                     |                                         |                                                                        |

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**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.**  
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/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