

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**205352Orig1s000**

**OTHER REVIEW(S)**

# Labeling Review for Aleve PM *Draft Labeling 2<sup>nd</sup> Amendment*

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**SUBMISSION DATES:** March 28, July 15, and December 6, 2013; January 9, 2013

**NDA/SUBMISSION TYPE:** NDA 205352/original NDA

**ACTIVE INGREDIENTS:** naproxen sodium 220 mg,  
diphenhydramine hydrochloride 25 mg

**DOSAGE FORMS:** tablet

**SPONSOR:** Bayer Healthcare – Consumer Care  
Priti C. Lad, PharmD  
973-254-4664

**REVIEWER:** Ayana K. Rowley, Pharm.D.

**TEAM LEADER:** Steven Adah, PhD

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## I. BACKGROUND

On January 6, 2014, FDA sent an information request to Bayer Healthcare regarding additional labeling recommendations from the Division of Medication Errors Prevention Analysis (DMEPA) labeling deficiencies. On January 9, 2014, the sponsor has provided revised labels to address the agency's recommended changes.

Submitted Labeling	Representative of Following SKUs
2-count pouch	none
20-, 40-, 80-count immediate containers and outer cartons	none

## II. REVIEWER'S COMMENTS

The following highlights each FDA recommendation with corresponding response from the sponsor denoting the revised changed. *NOTE: DMEPA has found that these labeling revisions are acceptable. The DMEPA labeling reviewer noted this on January 10, 2014 (via an internal email communication).*

- **FDA Requests: On the outer carton principal display panels of all package sizes**
  - Remove the symbol “+” from the PDP and spell out its intended meaning (i.e. “plus”). The plus symbol is an error prone symbol that has been mistaken for the number “4”. **SPONSOR Response: The “+” symbol has been removed and replaced with the word “plus” per FDA recommendation.**
  - Revise the background color so the proposed Aleve PM can be easily distinguished from currently marketed Aleve and Aleve-D products. We request that you use a different background color to adequately differentiate these products. The proposed (b) (4), and we are concerned that consumers will fail to recognize the differences between Aleve PM and Aleve or Aleve-D, and this confusion could lead to medication errors and result in adverse events. **SPONSOR Response: Per FDA's request, the background color on the cartons, immediate container labels and pouches has been revised to a darker solid color (b) (4) to better differentiate it from the existing Aleve products. Due to differences in computer screen and printer settings, the actual color of printed labeling components (i.e. cartons, immediate container labels) may be difficult to convey via .pdf images or printouts on paper. Therefore, on January 7, 2014, Bayer (Walsh) met briefly with FDA (Pham) so that samples of the colors to be used, as they will appear on the printed labeling components, could be viewed. Following this meeting, FDA (Pham) sent an e-mail on January 7, 2014 confirming the proposed color change was adequate.**

## III. RECOMMENDATIONS

DEMPEA found these labeling revisions to be acceptable (per email dated 1/10/2014). DNRD has no regulatory comments and found the labels to be acceptable for approval.

Issue an **APPROVAL** letter to the sponsor for the submitted Aleve PM labeling and request final printed labeling. Request that the sponsor submit final printed labeling (FPL) identical to: 2-count pouch and the 20-, 40-, and (b) (4) count immediate container (bottle, blister pack, lidding, etc.) and carton labels submitted on January 9, 2014.

## IV. SUBMITTED LABELING

The labels on the remaining pages of this labeling review were submitted and evaluated in this labeling review:

- 2-count pouch
- 20-, 40-, 80-count immediate containers and outer cartons.

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

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AYANA K ROWLEY  
01/10/2014

STEVEN A ADAH  
01/10/2014

# Labeling Review for Aleve PM *Draft Labeling Amendment*

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**SUBMISSION DATES:** March 28, July 15, and December 6, 2013

**NDA/SUBMISSION TYPE:** NDA 205352/original NDA

**ACTIVE INGREDIENTS:** naproxen sodium 220 mg,  
diphenhydramine hydrochloride 25 mg

**DOSAGE FORMS:** tablet

**SPONSOR:** Bayer Healthcare – Consumer Care  
Priti C. Lad, PharmD  
973-254-4664

**REVIEWER:** Ayana K. Rowley, Pharm.D.

**TEAM LEADER:** Steven Adah, PhD

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## I. BACKGROUND

On November 22, 2013, FDA sent an information request to Bayer Healthcare regarding a number labeling deficiencies. On December 6, 2013, the sponsor has provided revised labels to address the agency's recommended changes.

Submitted Labeling	Representative of Following SKUs
2-count pouch	none
20-, 40-, 80-count immediate containers and outer cartons	none

## II. REVIEWER'S COMMENTS

The following highlights each FDA recommendation with corresponding response from the sponsor denoting the revised changed. These are acceptable.

- **FDA Requests: On the outer carton principal display panels and the immediate container front panels of all package sizes**

- Remove the statement (b) (4) or replace it with a statement that makes it clear that the product (b) (4) and does not use the phrase (b) (4) **SPONSOR Response: Statement has been removed.**
- Break the statement, “sleep aid [plus] 12 hour pain relieving strength of Aleve” at a different point, such as between [plus] and 12, or show in some way that it is a single statement. **SPONSOR Response: The statement has been revised as suggested.**
- Add an asterisk next to “Caplets” and an asterisk before the definition of the dosage form, “capsule-shaped tablets.” **SPONSOR Response: The asterisk has been added as requested.**

- **FDA Request: On the outer carton and 2-count pouch Drug Facts and the immediate container back panels of all package sizes**

- Remove (b) (4) from *Questions or comments?* or (b) (4) for review as labeling. **SPONSOR Response: Reference to (b) (4)**
- **FDA Requests: On the 20-, 40-, and 80-count outer cartons**
  - A banner stating, “New” appears on the upper right corner of the Principal Display Panel. Language should be added to explain that the product itself is new. The banner may remain in place for 6 months of marketing. **SPONSOR Response: The banner has been revised to now read, "New Product". It will be removed after 6 months of marketing.**
  - Add an instruction to the outer carton to read and keep the outer carton. This could stand-alone or be added under *Other information*. **SPONSOR Response: The statement found under "Other Information" has been revised to: “[bullet] read all warnings and directions before use. Keep outer carton.”**
- **FDA Request: On the 20-, 40-, and 80-count immediate container labels**
  - Add “Drink a full glass of water with each dose” to **Directions** on the immediate containers or change (b) (4) to (b) (4) **SPONSOR Response: The statement has been revised to read, (b) (4)**
- **FDA Request: On the 20- and 40-count immediate container labels and the 2-count pouch**
  - Add a period at the end of the symptoms of allergic reaction, as follows, “...[bullet] rash [bullet] blisters [insert period] If an allergic reaction...” to separate the list from the following sentence. **SPONSOR Response: The period has been added.**

- FDA Request: On the 80-count immediate container label
  - Consider using a peel-back Drug Facts label so that additional information, including the complete allergy alert, will be readily available at the point of use. **SPONSOR Response: A revised label structure has been developed. The complete allergy alert now appears at point of use. NOTE: The sponsor has chosen to develop a peel off label that is similar to the 20- and 40-count outer cartons.**
- **FDA Requests: On the 20-count outer carton**
  - Increase the spaces between bullets and preceding text to at least two square ems as required in 201.66(d)(4). **SPONSOR Response: The spacing has been increased as requested.**
  - Remove the parentheses from the signs and symptoms of stomach bleeding under *Stop use and ask a doctor if* to conform with 201.326(a)(2)(iii)(C). **SPONSOR Response: The parentheses have been removed as requested.**
- **FDA Request: On the 2-count pouch**
  - Show the locations of the lot number and expiration date as required in 21 CFR 201.17, 211.132, and 201.18. **SPONSOR Response: The artwork for the pouch now indicates where the lot number and expiration date will be included.**

### III. RECOMMENDATIONS

Issue an **APPROVAL** letter to the sponsor for the submitted Aleve PM labeling and request final printed labeling. Request that the sponsor submit final printed labeling (FPL) identical to: 2-count pouch and the 20-, 40-, and (b)(4) count immediate container (bottle, blister pack, lidding, etc.) and carton labels submitted on December 6, 2013

### IV. SUBMITTED LABELING

The labels on the remaining pages of this labeling review were submitted and evaluated in this labeling review:

- 2-count pouch
- 20-, 40-, 80-count immediate containers and outer cartons.

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

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/s/  
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AYANA K ROWLEY  
12/10/2013

STEVEN A ADAH  
12/11/2013

# Labeling Review for Aleve PM *Draft Labeling*

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**SUBMISSION DATES:** March 28, 2013 and July 15, 2013

**NDA/SUBMISSION TYPE:** NDA 205352/original NDA

**ACTIVE INGREDIENTS:** naproxen sodium 220 mg,  
diphenhydramine hydrochloride 25 mg

**DOSAGE FORMS:** tablet

**SPONSOR:** Bayer Healthcare – Consumer Care  
Priti C. Lad, PharmD  
973-254-4664

**REVIEWER:** Kathleen M. Phelan, RPh

**TEAM LEADER:** Steven Adah, PhD

---

## I. BACKGROUND

Bayer Healthcare submitted an NDA for Aleve PM on March 28, 2013. The submission included a 2-count pouch but did not include an outer carton for this SKU. In the 74-Day Letter, FDA asked how the 2-count pouch would be displayed and sold. In a response letter dated July 15, the sponsor explained that the 2-count pouch would be (b) (4) incorporating the approved Drug Facts labeling into the design of the external carton.” FDA also asked for a list of all SKUs to be sold under the NDA and labels for all SKUs. The sponsor replied that the 20-, 40-, and 80-count packages were all of the SKUs currently intended for marketing under this NDA. The labels were in the March 28 submission.

As part of IND 103,407 for Aleve PM, Bayer Healthcare had submitted Drug Facts content on August 27, 2012, and mock-ups of principal display panels on October 5, 2012 for comment. FDA provided comments to the sponsor at an October 9, 2012 teleconference.

Submitted Labeling	Representative of Following SKUs
2-count pouch	none
20-, 40-, 80-count immediate containers and outer cartons	none

Labels were compared to the Advil PM labels (dated February 4, 2013) that were approved as part of NDA 21393/S-012. Also, the proposed Drug Facts content was compared to the Drug Facts content submitted under IND 103,407 on August 27, 2012, the comments provided in the October 9, 2012 teleconference, the Medical Officer review of 103,407 signed into DARRTS on October 9, 2012, and the labeling reviews of 103,407 signed into DARRTS on October 3 and December 4, 2012. Drug Facts format was checked for compliance with format requirements in 21 CFR 201.66.

## II. REVIEWER'S COMMENTS

### A. All SKUs

#### i. Outer Carton Label Outside Drug Facts –Principal Display Panel

##### Immediate Container and 2-count pouch front labels

- a. Just below the trade name is an image of a moon with the words, (b) (4). This is not acceptable. Any statement of the product's effects must include both intended effects: pain relief and sleep. (b) (4)

(b) (4) he statement should be removed or changed to include both sleep and pain and to remove the term (b) (4)

- b. The statement, “sleep aid + 12 hour pain relieving strength of Aleve” appears on the lower left. As discussed in the December 4, 2012, addendum labeling review for IND 103,407, this statement is acceptable. However, several members of the review team saw this as two statements because of how it is broken on the PDP, between “pain” and “relieving.” The statement should be broken differently or shown in a way that clarifies that it is one statement.
- c. In the net quantity of contents, an asterisk should be added after “caplets” and before “capsule-shaped tablets” to link the definition to the dosage form.
- d. “NSAID” appears in the statement of identity and is formatted as required in 201.326(a)(2)(i). This is acceptable.

#### ii. Outer Carton and 2-count pouch Drug Facts

##### Immediate Container back labels

###### a. Questions or comments?

After the phone number is, (b) (4).” It is DNCE policy that any (b) (4) to which the consumer is directed by labeling must be submitted for review as labeling. The sponsor should be asked to submit any (b) (4) to which this (b) (4)

#### iii. Outer Carton and 2-count pouch Drug Facts

##### a. Purposes

The singular “Purpose” that was in the IND Drug Facts was changed to “Purposes” as requested. This is acceptable.

*b. Uses*

The labeled uses are the same as those approved for Advil PM. These are, “for relief of occasional sleeplessness when associated with minor aches and pains” and “helps you fall asleep and stay asleep.” Reviewers from other disciplines will determine whether the submitted data support these uses.

*c. Warnings*

The bulleted statements under **Ask a doctor before use if** are in a different order than in the IND Drug Facts submitted on August 27, 2012. The revised order is identical to that on the Advil PM approved label. This is acceptable.

Under **Ask a doctor or pharmacist before use if you are,** (b) (4) from the IND Drug Facts was changed to “under a doctor’s care for any serious condition,” as requested in the IND Drug Facts review of October 2012. This is acceptable.

*d. Other information*

The label states, “Each caplet contains: sodium 20 mg.” The chemistry reviewer has determined that this is accurate.

*e. Inactive ingredients*

Compared with the IND Drug Facts, carnauba wax has been listed as the first ingredient and purified water has been listed between povidone and talc; (b) (4) has been changed to FD&C blue #2 aluminum lake. The chemistry reviewer has determined that this inactive ingredient listing is correct.

**B. 20-, 40-, 80-count capsule-shaped tablets**

**i. Outer Carton Label Outside Drug Facts**

- a.* A banner stating, “New” appears on the upper right corner of the Principal Display Panel. It is DNCE policy that “new” banners say what is new. Language should be added to explain that the product itself is new. The banner may remain in place for 6 months on the market.
- b.* Lot number (21 CFR 201.18), expiration date (21 CFR 201.17 and 211.137), manufacturer address (21 CFR 201.1(i)), and country of origin (19 CFR 134) are present. This is acceptable.
- c.* The outer carton does not advise the consumer to retain the carton for complete Drug Facts information. Although “See Carton For Full Information” is on the immediate container, the consumer may already have discarded the outer carton before seeing this statement and the immediate container labels have much less information than the outer cartons. The sponsor should place a statement that advises the consumer to retain the outer carton on the outer carton. This could be free-standing or could be added under *Other information*.

**ii. Immediate Container Label****a. Front Panel**

Lot and expiration date location is noted as required in 21 CFR 201.17, 211.132, and 201.18. This is acceptable.

**b. Back Panel**

Active ingredients and Stomach bleeding warning (21 CFR 201.326(a)(2)(iii)(A)) are present. This is acceptable.

**c. Directions**

*Directions* say to (b) (4) The full Drug Facts *Directions* say, “drink a full glass of water with each dose.” The instruction to drink a full glass of water with each dose is a safety precaution because there have been reports of Aleve tablets being stuck in the throat. The direction is required for safe use of the product. “Drink a full glass of water with each dose” should be added to *Directions* on the immediate containers or the existing statement should be revised to (b) (4)

**C. 20-, 40-count capsule-shaped tablets****i. Immediate Container Label****a. Allergy alert**

A period should be added at the end of the symptoms of allergic reaction, as follows, “...• rash • blisters[insert period] If an allergic reaction...” to separate the list from the following sentence. Other statements are not followed by periods but in those cases, the following information begins with bolded type, which provides a visual break.

**D. 40-, 80-count capsule-shaped tablets****i. Outer Carton Label - Drug Facts****a. General**

Drug Facts comply with format requirements in 21 CFR 201.66. This is acceptable.

**E. 2-count capsule-shaped tablets pouch (immediate/outer container)****i. Outside Drug Facts**

- a.** “Do not use if pouch is torn or open” appears on the front panel with the trade name. This tamper-evident statement provides important safety information and putting it in a prominent place on the label as required in 21 CFR 211.132(c) is acceptable.
- b.** The manufacturer address (21 CFR 201.1(i)), and country of origin (19 CFR 134) are present. This is acceptable.
- c.** The location of the lot number and expiration date is not noted as required in 21 CFR 201.17, 211.132, and 201.18. This is not acceptable.

**ii. Drug Facts****a. Warnings**

A period should be added at the end of the symptoms of allergic reaction, as follows, "...• rash • blisters[insert period] If an allergic reaction..." to separate the list from the following sentence. Other statements are not followed by periods but in those cases, the following information begins with bolded type, which provides a visual break.

**b. Questions or comments**

The heading has been changed from the Drug Facts in the IND from "Questions or comments?" to (b) (4) Either heading is allowed by 201.66(c)(9). This is acceptable.

**F. 20-count capsule-shaped tablets****i. Outer Carton Drug Facts Label****a. General**

The format specifications in 201.66(d)(10), for packages that require more than 60% of available area for Drug Facts, have been used. This is acceptable.

Bullets are not separated from subheadings and other preceding text by at least two square "ems" as required in 201.66(d)(4). This requirement is not negated in 201.66(d)(10)(iv). This is not acceptable.

**b. Warnings**

Under **Stop use and ask a doctor if**, the signs of stomach bleeding are in parentheses. Parentheses are not included in 201.326(a)(2)(iii)(C). The sponsor should remove the parentheses.

**G. 80-count capsule-shaped tablets****i. Immediate Container Label****a. Back Panel**

The allergy alert does not include the signs skin reddening, rash, or blisters. Nor does it include the instruction, "If an allergic reaction occurs, stop use and seek medical help right away." Regulations do not require the allergy alert on the immediate container label, but the current label omits important signs of allergic reaction as well as actions to take if an allergic reaction occurs. The sponsor should be encouraged to use peel-back Drug Facts labeling to accommodate more information, including the full allergy alert. Each use carries risks that could potentially be lessened by providing more information at the point of use.

**III. RECOMMENDATIONS**

We currently recommend a Complete Response action pending the resolution of the following labeling deficiencies:

- On the outer carton principal display panels and the immediate container front panels of all package sizes

- Remove (b) (4) or replace it with a statement that makes it clear that the product is indicated to relieve difficulty sleeping as well as pain and does not use the phrase (b) (4)
- Break the statement, “sleep aid [plus] 12 hour pain relieving strength of Aleve” at a different point, such as between [plus] and 12, or show in some way that it is a single statement.
- Add an asterisk next to “Caplets” and an asterisk before the definition of the dosage form, “capsule-shaped tablets.”
- On the outer carton and 2-count pouch Drug Facts and the immediate container back panels of all package sizes
  - Remove (b) (4) from *Questions or comments?* or submit all (b) (4) to which this (b) (4) for review as labeling.
- On the 20-, 40-, and 80-count outer cartons
  - A banner stating, “New” appears on the upper right corner of the Principal Display Panel. Language should be added to explain that the product itself is new. The banner may remain in place for 6 months of marketing.
  - Add an instruction to the outer carton to read and keep the outer carton. This could stand alone or be added under *Other information*.
- On the 20-, 40-, and 80-count immediate container labels
  - Add “Drink a full glass of water with each dose” to **Directions** on the immediate containers or change (b) (4) to (b) (4)
- On the 20- and 40-count immediate container labels and the 2-count pouch
  - Add a period at the end of the symptoms of allergic reaction, as follows, “...• rash • blisters[insert period] If an allergic reaction...” to separate the list from the following sentence.
- On the 80-count immediate container label
  - Consider using a peel-back Drug Facts label so that additional information, including the complete allergy alert, will be readily available at the point of use.
- On the 20-count outer carton,
  - Increase the spaces between bullets and preceding text to at least two square ems as required in 201.66(d)(4).
  - Remove the parentheses from the signs and symptoms of stomach bleeding under *Stop use and ask a doctor if* to conform with 201.326(a)(2)(iii)(C).
- On the 2-count pouch
  - Show the locations of the lot number and expiration date as required in 21 CFR 201.17, 211.132, and 201.18.

Issue a communication to the sponsor that includes these deficiencies in order to initiate labeling negotiations.

**IV. SUBMITTED LABELING**

The labels on the remaining pages of this labeling review were submitted and evaluated in this labeling review:

- 2-count pouch
- 20-, 40-, 80-count immediate containers and outer cartons.

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KATHLEEN M PHELAN  
11/20/2013

STEVEN A ADAH  
11/20/2013

**Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology  
Office of Medication Error Prevention and Risk Management**

**Addendum to Previous Label and Labeling Review**

Date: November 12, 2013

Reviewer: Chi-Ming (Alice) Tu, PharmD  
Division of Medication Error Prevention and Analysis

Team Leader: Jo Wyeth, PharmD  
Division of Medication Error Prevention and Analysis

Drug Name and Strength: Aleve PM (Naproxen Sodium and Diphenhydramine Hydrochloride) Caplets, 220 mg/25 mg

Application Type/Number: NDA 205352

Submission Number: 1

Applicant/Sponsor: Bayer

OSE RCM #: 2013-788-1

\*\*\* This document contains proprietary and confidential information that should not be released to the public.\*\*\*

This memo provides an addendum to our previous review of the Aleve PM container labels and carton labeling, dated September 26, 2013<sup>1</sup>. Specifically, we are making one additional recommendation to be implemented prior to approval of NDA 205352:

A. Comments to the Applicant

1. Revise the background color so the proposed Aleve PM can be easily distinguished from currently marketed Aleve and Aleve-D products. We request that you use a different background color to adequately differentiate these products. The proposed  (b) (4)  medication errors and result in adverse events.

If you have questions or need clarifications, please contact Abiola Olagundoye, OSE Safety Regulatory Project Manager, at 301-796-3982.

**BASIS FOR THE ADDITIONAL RECOMMENDATION**

 (b) (4)



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<sup>1</sup> Tu, A. Label, labeling, and packaging review: Aleve PM (Naproxen Sodium and Diphenhydramine HCl (NDA 205352), Silver Spring (MD): Food and Drug Administration, Center for Drug Research and Evaluation, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis; 2013 Sep 26. 7 p. Report No.: RCM 2013-788.

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CHI-MING TU  
11/12/2013

JO H WYETH  
11/12/2013

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology**

**Integrated Review**

**Date:** October 29, 2013

**Reviewer(s):** Carolyn Volpe, Pharm.D., Safety Evaluator  
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**Division Director(s):** Judy Staffa, Ph.D., R.Ph., Division Director  
Division of Epidemiology II  
  
Scott Proestel, M.D., Division Director  
Division of Pharmacovigilance II

**Product Name(s):** Aleve PM (naproxen sodium/diphenhydramine hydrochloride)

**Subject:** Accidents; Abuse/Misuse

**Application Type/Number:** NDA 205352

**Submission Number:** Original Submission

**Applicant/Sponsor:** Bayer Healthcare

**OSE RCM #:** 2013-1322

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## EXECUTIVE SUMMARY

This review evaluates post-marketing databases and published literature for an association between accidents, abuse, and misuse with over-the-counter (OTC) diphenhydramine (DPH). This review also includes an analysis of the drug utilization patterns of oral OTC DPH-containing products from 2007 to 2012. The Division of Nonprescription Clinical Evaluation (DNCE) requested this review to inform a New Drug Application (NDA) submitted by Bayer Healthcare (Bayer) for a naproxen (NXN) and DPH combination product under the proposed trade name “Aleve PM.”

A search of the FDA Adverse Event Reporting System (FAERS) retrieved relatively few cases of accidents (n=37) associated with DPH use despite decades of marketing and widespread use of DPH. Of the 37 cases, 18 cases reported injuries related to motor vehicles accidents and 20 cases reported injuries as a result of a fall. Injuries in these cases ranged from non-serious injuries (e.g., “sore ribs and nose”) to serious injuries (e.g., bone fractures, head injuries, ruptured vertebrae). Two cases reported a fatal outcome; both cases involved motor vehicle accidents.

From the total DPH FAERS data, death was reported as an outcome in 36% (4637/12538) of the cases. A majority of cases reporting an outcome of death with DPH use were reported in the intentional overdose case series (71%, 3315/4637). Of the cases that reported DPH as a primary suspect in the intentional overdose case series, the acetaminophen + DPH combination was reported in 35% of cases and ibuprofen + DPH was reported in 3% of cases. The intentional and unintentional overdose case series were not assessed for a causal association with DPH; however, the majority of cases (80% of cases in the intentional overdose case series and 70% of cases in the unintentional overdose case series) reported using or abusing multiple medications or recreational substances (including alcohol) along with DPH.

A search of the literature yielded only 2 relevant observational studies regarding the association between DPH-containing products, and misuse/abuse or suicidality. Sinyor et al., 2012, found that DPH was the most prevalent drug detected in lethal amounts post-mortem in suspected suicides in Toronto, Canada from 1998 to 2007. Jaffe et al., 2004, showed a clustering of responses to drug abuse liability questions specific only to sedative/hypnotic drugs among drug users admitted to a drug treatment facility. Of all the drugs that were a part of the survey, the antihistamines (of which DPH was one of two) showed the lowest abuse liability compared to the other drugs. These studies were limited by their lack of control groups, and their biased selection of subjects which precludes generalization to larger populations.

The misuse and abuse of DPH-containing products was also assessed via nationally projected estimates of emergency department (ED) visits associated with DPH exposure using the Drug Abuse Warning Network (DAWN), and National Electronic Injury Surveillance System – Cooperative Adverse Drug Event Surveillance (NEISS-CADES).

The DAWN data showed that single-ingredient DPH was associated with a greater frequency of misuse/abuse and suicide attempt (SA) ED visits than DPH in combination with an analgesic compound, e.g. acetaminophen and ibuprofen, from 2004 to 2011. DAWN ED visit estimates related to misuse/abuse and SAs increased during that time period for not only single-ingredient DPH, but also DPH + acetaminophen.

When the DAWN ED visit data were put in the context of the sales for DPH-containing products, visits associated with single-ingredient DPH were approximately equivalent to DPH + acetaminophen relative to their sales. DPH-containing products had fewer visits than the chlorpheniramine/acetaminophen combination products after adjusting for its utilization for all

but one of the years. Estimates for DPH + acetaminophen appeared to have slightly higher amount of SA ED visits relative to its sales compared to single-ingredient DPH from 2007-2011.

The NEISS-CADES data depicting unintentional overdoses associated with DPH-containing drugs from 2004 through 2011 show an overall increasing trend over the entire time period. On average, more than half of all the estimated ADEs from DPH-containing products are a result of unintentional overdoses.

This review shows that DPH-containing products are associated with accidents, misuse/abuse, suicide attempts, and unintentional overdoses; however, the frequencies of these events are relatively modest given its wide OTC utilization. There is potential for abuse/misuse and suicide attempts with DPH, but the data suggest a lower risk of these events compared to drugs with a known high potential for abuse/misuse (e.g., hydrocodone-combination products). Furthermore, the data do not show that the risk is disproportionate, given its widespread availability.

The introduction of this new DPH analgesic combination product would likely result in similar levels of abuse/misuse and accidents seen with other DPH analgesic combination products. In addition, the current and proposed labeling for DPH sleep aid products describes the CNS effects of DPH and cautions on driving or operating machinery with these products.

This review did not identify any new issues with diphenhydramine hydrochloride. OSE agrees with the proposed labeling for CNS effects and effects on driving submitted with NDA 205352 (naproxen sodium + diphenhydramine hydrochloride).

## **1 INTRODUCTION**

This review evaluates post-marketing databases and published literature for an association between accidents, abuse, and misuse and over-the-counter (OTC) diphenhydramine (DPH). This review also includes an analysis of the drug utilization patterns of oral OTC DPH-containing products from 2007 to 2012. The Division of Nonprescription Clinical Evaluation (DNCE) requested this review to inform a New Drug Application (NDA) submitted by Bayer Healthcare (Bayer) for a naproxen (NXN) and DPH combination product under the proposed trade name “Aleve PM.”

### **1.1 BACKGROUND**

On March 20, 2013, Bayer submitted a New Drug Application (NDA) for Aleve PM (naproxen sodium 220 mg + diphenhydramine hydrochloride 25 mg). The proposed indication is for the relief of occasional sleeplessness associated with minor aches and pains. As part of the NDA, Bayer submitted post-marketing adverse event data for NXN and DPH. After evaluating the data, overdose and misuse were identified in greater frequency than other adverse events for DPH; however, Bayer did not identify any new safety signals.

DNCE requested an evaluation of abuse tendencies and suicidality in regards to DPH to aid the decision of whether to approve this application. In the NDA submission, DPH has been attributed to a number of adverse events (AE) and deaths from 2004-2011. For instance, Bayer’s summary of publicly available FDA Adverse Event Reporting System (FAERS) data for DPH noted a large percentage of cases with fatal outcomes (43.9%, 2476/5644) and non-fatal serious outcomes (45.9%, 2590/5644). Due to the limited data on the publicly available FAERS website, Bayer was unable to fully evaluate these reports.

In addition, the FDA has worked with the National Transportation Safety Board (NTSB) since 2000 to increase public awareness about medications that may increase the risk of motor vehicle

accidents (MVA). The 1<sup>st</sup> generation antihistamines, including DPH, are among these medications. Since 2006, the FDA has released several communications, geared towards consumers, addressing the safety of taking certain medications and driving, including, “Driving When You Are Taking Medications”<sup>1</sup> and “Some Medications & Driving Don’t Mix.”<sup>2</sup> Also, there is an FDA website listing OTC drugs that can affect driving.<sup>3</sup> DNCE requested this review also focus on accidents that are associated with DPH use.

Both NXN and DPH have been approved as single-ingredient products for a variety of indications and in combination with other compounds, but not in combination with each other. Both drugs are available as prescription and OTC products.

DPH is a 1<sup>st</sup> generation H<sub>1</sub> antihistamine, and is used for a variety of indications including, but not limited to, insomnia, motion sickness, and symptoms associated with allergies, hay fever or the common cold. First generation H<sub>1</sub> antihistamines are lipophilic with ethylamine moieties that are able to cross the blood-brain barrier and occupy the central nervous system (CNS) H<sub>1</sub> receptor sites.<sup>4</sup> This receptor site binding leads to impairment of CNS function including decreased alertness, cognition, and psychomotor activity. The 1<sup>st</sup> generation antihistamines may also cause adverse events through other mechanisms, such as antimuscarinic effects (increased dry mouth and urinary retention).<sup>5</sup> DPH overdose in adults can lead to extreme drowsiness, confusion, delirium, coma, and respiratory depression. However, overdose in children and infants can lead to paradoxical CNS excitation with irritability, hyperalertness, insomnia, hallucinations, and seizures.<sup>4</sup>

## 1.2 REGULATORY HISTORY

Antihistamines were first synthesized in 1937, and first introduced for clinical use in the United States in 1942. DPH was first approved by the FDA on March 4, 1946. There are now many DPH products available by prescription and OTC, including injectables and oral dosage forms, which are regulated by NDAs and under the monograph system. Currently, Advil PM (ibuprofen + diphenhydramine) is the only OTC DPH product approved under an NDA. The NDAs (different dosage forms are approved) for this product were approved December 21, 2005.

All other OTC DPH products are marketed under either the Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products for Over-The-Counter Human Use (21CFR341) monograph or the Nighttime Sleep-Aid Drug Products for Over-The-Counter Human Use (21CFR338) monograph. Both of these monographs are final, and both were published December 9, 1992.

## 1.3 PRODUCT LABELING

The proposed Drug Facts label submitted March 20, 2013, as part of the NDA for Aleve PM is identical to the currently FDA approved Advil PM Drug Facts label.<sup>6</sup> The following sections of the Drug Facts label are identical between the proposed Aleve PM label and Advil PM label:

- Indications: 1) relief of occasional sleeplessness when associated with minor aches and pains and 2) helps you fall asleep and stay asleep.
- Dosing: adults and children 12 years and older take 2 caplets at bedtime; do not take more than 2 caplets in 24 hours
- Warnings (listed specifically for DPH):
  - Do not use with any other product containing DPH, even one used on the skin
  - Ask a doctor or pharmacist before use if you are taking sedatives or tranquilizers, or any other sleep-aid; taking any other antihistamines
  - When using this product: drowsiness will occur; avoid alcoholic drinks; do not drive a motor vehicle or operate machinery

- Stop use and ask a doctor if sleeplessness persists continuously for more than 2 weeks. Insomnia may be a symptom of a serious underlying medical illness

This labeling is also consistent with the required monograph labeling for DPH; however, dosing for DPH from the Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic monograph allows DPH hydrochloride to be dosed as 25 to 50 mg every 4 – 6 hours, not to exceed 300 mg daily (DPH citrate 38 to 76 mg every 4 – 6 hours, not to exceed 456 mg daily).

## 2 METHODS AND MATERIALS

### 2.1 DRUG UTILIZATION DATA SOURCES

The proprietary OTC International Market Tracking (OTCIMS) database was used to provide the nationally estimated number of bottles/packages of oral OTC DPH-containing products sold from various U.S. outpatient retail store outlets for 2007 through 2012. Although these data show the amount of product sold to consumers, direct patient use of OTC products is not available since the actual or intended user is not captured. These data are meant to provide context to the counts of abuse/misuse related outcomes associated with DPH-containing products from other sources. Similar data were also obtained for single-ingredient chlorpheniramine (CPH) and CPH + acetaminophen for comparison. See *Appendix A* for descriptions of the drug utilization data source and vendor data collection methods.

### 2.2 REVIEW OF ACCIDENTS

#### 2.2.1 FAERS Case Definition for Accidents

For the accidents case series (section 3.3.1), we included all cases that reported the following:

- oral DPH as the only suspect medication
- domestic case
- a temporal association to DPH or a laboratory test showing a detectable level of DPH

Cases were excluded if:

- multiple medications were reported as suspect medications
- recreational drugs or alcohol were reportedly used
- accidents or injuries resulted from a non-drug cause
- the injuries resulted from organ damage (e.g., liver *injury*)
- no accident or injury was reported

#### 2.2.2 FAERS Search Strategy for Accidents

The FDA Adverse Event Reporting System (FAERS) was searched with the strategy described in Table 1.

<b>Table 1. FAERS Search Strategy*</b>	
Date of search	July 11, 2013
Time period of search	January 1, 1969 <sup>†</sup> - July 10, 2013
Product Terms	Active Ingredients: Diphenhydramine Diphenhydramine hydrochloride Diphenhydramine citrate
MedDRA Search Terms	Preferred Terms: Accident; Accident at home; Accident at work; Fall; Impaired

	Driving Ability; Injury; Road Traffic Accident
Other criteria	Serious Only

\* See Appendix B for description of the FAERS database.

^ Search of the entire FAERS database

### 2.2.3 Data Mining Search Strategy for Accidents

The Empirica Signal database was searched with the strategy described in Table 2.

<b>Table 2. Data Mining Search Strategy*</b>	
Data Refresh Date	August 10, 2013
Product Terms	Diphenhydramine
Empirica Signal Run Name	Ingredient (S), ID 10504
MedDRA Search Terms	Preferred Terms: Accident; Accident at home; Accident at work; Fall; Impaired Driving Ability; Injury; Road Traffic Accident
Other criteria	None; all reports (serious and non-serious) included

\* See Appendix B for description of Data Mining of FAERS using Empirica Signal.

## 2.3 REVIEW OF ABUSE AND MISUSE

### 2.3.1 Literature review

Two databases were used to search the literature for this review, the National Library of Medicine's PubMed web database and the EMBASE database. On July 1, 2013, the literature database search was conducted to identify references related to the use of DPH, and abuse, addiction or suicide. The PubMed search included all available published literature (no years of publication were excluded) and the following search criteria were used:

**((((diphenhydramine) AND overdose) OR diphenhydramine abuse) OR diphenhydramine suicide) OR diphenhydramine death) OR diphenhydramine addiction).** The search was limited to human subjects and reports written in English. This search yielded 401 articles. When sorted by epidemiological or observational study, the search yielded 35 articles.

The EMBASE search included all available published literature, and the following search criteria were used:

**'diphenhydramine'/exp AND ('suicide'/exp OR 'addiction'/exp OR 'abuse'/exp OR 'overdose'/exp) AND [humans]/lim AND [english]/lim.** The "exp" command allows for searches of related words associated with the root word. This search was limited to human subjects and reports written in English, as well. This search yielded 1564 papers. When sorted by "study design" (*clinical trial, controlled clinical trial, controlled study, drug surveillance program, major clinical study, meta analysis, randomized controlled trial, retrospective study, and systematic review*) and "disease" (*adverse drug reaction, drug dependence, drug overdose, intoxication and withdrawal syndrome*) filters, the search yielded 207 articles.

All 35 PubMed and 207 EMBASE articles were reviewed and included based on their relevancy to the objective of this assessment – understanding the association between DPH and misuse/abuse or suicidality. If the published studies did not explicitly examine DPH and abuse/misuse-related outcomes or suicidality they were excluded.

### 2.3.2 Drug Abuse Warning Network (DAWN)

The Drug Abuse Warning Network (DAWN) was used to estimate the number of misuse and abuse cases associated with DPH. DAWN, administered by the Substance Abuse and Mental Health Services Administration (SAMHSA), was a public health surveillance system that reported on drug-related ED visits through 2011. DAWN captures drug-related ED visits by retrospective review of medical records in a national sample of hospitals. Hospitals eligible for DAWN include non-Federal, short-stay, general and surgical hospitals that operate 24-hour EDs. ED visits are included via a multistage sampling design where hospitals are chosen by stratified simple random sampling with oversampling in specific metropolitan areas, and then days of operation are selected systematically within each hospital's ED. National estimates of ED visits are generated after adjustments and weights are applied to the aggregate data submitted by these sampled hospitals. In order to categorize ED case types related to misuse and abuse, SAMHSA developed an operational construct referred to as All Misuse/Abuse (AllMA). AllMA cases include:

- suicide attempts only if illicit drugs were involved
- overmedication
- patient took a medication not prescribed for them
- detoxification seeking only if illicit drugs were involved
- malicious poisoning
- illicit drug or alcohol-related ED visits
- substance abuse

DAWN also captures information regarding all deaths, and specifically suicide deaths, associated with drug substances for 13 States: Delaware (DE), Massachusetts (MA), Maryland (MD), Maine (ME), New Hampshire (NH), New Mexico (NM), Oklahoma (OK), Oregon (OR), Rhode Island (RI), Utah (UT), Virginia (VA), Vermont (VT), and West Virginia (WV). These data are not nationally representative; they are actual counts, gathered from medical examiner and coroner reports. DAWN death data excludes decedents ages five and younger, and is suppressed if the count is less than four for confidentiality reasons. Death data are available through 2010.

Cases were selected based on the following criteria-

- 1) ED visit date between January of 2004 – December of 2011
- 2) Cases were classified as:
  - All Misuse and Abuse (AllMA) cases involving DPH
  - Suicide attempts involving DPH
  - Completed suicides involving DPH from the 13 states (until 2010)
  - Deaths (excluding suicide) involving DPH from the 13 states (until 2010)
- 3) At least one of the drugs linked to the ED visit was a DPH-containing product in either of the following drug classes:
  - Central Nervous System (CNS) agents
    - Anxiolytics, sedatives, hypnotics, and miscellaneous
    - Analgesic combinations

- Respiratory agents
  - Antihistamines
  - Upper respiratory combinations

See *Appendix C*, for a list of the drugs included in the analysis (topical agents were excluded). There was no exclusion criteria applied to the selection of cases. Due to substantial methodological changes that took place with DAWN data collection efforts in 2004, data from prior years is difficult to compare to data after the changes were implemented and thus 2004 was selected as the starting point of all analyses. Additionally, DAWN data collection ended in 2011 and estimates are not available for 2012 or later.

It is important to note that if error in the estimate exceeds a predefined threshold, or if the estimate is based on less than 30 ED visits, a national estimate cannot be generated as it may not be reliable.

ED visit data were also obtained for hydrocodone-combination (HC) products, single-ingredient CPH, and CPH + acetaminophen as these products were used as comparators for DPH. HC products were chosen to represent the higher end of the abuse spectrum with known abuse liability. Single-ingredient CPH and CPH + acetaminophen were chosen based on their similarity in indication to DPH-containing drugs. All three comparators are useful in providing a frame of reference for DPH along the abuse liability continuum.

### **2.3.3 National Electronic Injury Surveillance System-Cooperative Adverse Drug Event Surveillance (NEISS-CADES)**

Potential abuse cases were also obtained from the National Electronic Injury Surveillance System – Cooperative Adverse Drug Event Surveillance, or NEISS-CADES, a data resource capturing adverse drug events that lead to emergency department visits in a nationally representative sample of hospitals. NEISS-CADES, a joint endeavor of the Centers for Disease Control and Prevention (CDC), the Consumer Product Safety Commission, and the Food and Drug Administration (FDA), is a database that captures ADEs that result in an ED visit. Data is collected from a nationally representative sample of 63 hospitals that operate 24-hour EDs in the U.S. ADE cases are identified using clinical records where the physician explicitly links the use of a drug, or a drug-specific effect, to the condition that resulted in the ED visit. ADE outcomes collected include:

- allergic reactions
- adverse effects
- unintentional ODs
- accidental ingestions
- secondary effects, e.g. choking, or sedative effects precipitating a fall

Note that intentional self-harm, drug therapeutic failures, drug withdrawal, and drug abuse are not included in the NEISS-CADES database. However, since intentionality is based on physician judgment, it is possible that intentional abuse/misuse OD cases could be misclassified as unintentional. These data have therefore been included in order to present the most complete picture of all possible intentional DPH-related adverse events.

Follow-up visits associated with prior ADEs and drugs administered in the ED are excluded. Up to 2 drugs can be recorded for each ADE. National estimates can only be reported if there are

≥20 cases on which to base the estimate, the coefficient of variation is < .30, and the estimate is ≥ 1,200.

Cases were selected based on the following query criteria-

- 1) ED visit date between January of 2004 – December of 2011
- 2) Cases were classified as:
  - Adverse Drug Events (ADEs)
  - Unintentional overdose (OD) ADEs
- 3) DPH was at least one of the drugs linked to the ED visit recorded in “generic” category field 1 or 2, and/or “drug category” field 1 and 2

### 2.3.4 FAERS Search Strategy for Abuse/Misuse

The FDA Adverse Event Reporting System (FAERS) was searched with the strategy described in Table 3.

<b>Table 3. FAERS Search Strategy</b>	
Date of search	July 11, 2013
Time period of search	January 1, 1969 <sup>^</sup> - July 10, 2013
Product Terms	Active Ingredients (All queries): Diphenhydramine Diphenhydramine hydrochloride Diphenhydramine citrate
MedDRA Search Terms	Preferred Terms: 1) Intentional Overdose Query: Drug Abuse; Intentional Drug Misuse; Intentional Overdose; Overdose; Completed Suicide; Toxicity to Various Agents 2) Unintentional Overdose Query: Accidental Overdose;

<sup>^</sup> Search of the entire FAERS database

### 2.3.5 Data Mining Search Strategy for Abuse/Misuse

The Empirica Signal database was searched with the strategy described in Table 4.

<b>Table 4. Data Mining Search Strategy*</b>	
Data Refresh Date	August 10, 2013
Product Terms	Diphenhydramine
Empirica Signal Run Name	Ingredient (S), ID 10504
MedDRA Search Terms	Preferred Terms: 1) Intentional Overdose Query: Completed Suicide; Drug Abuse; Intentional Drug Misuse; Intentional Overdose; Overdose, Toxicity to Various Agents; 2) Unintentional Overdose Query: Accidental Overdose;
Other criteria	None; all reports (serious and non-serious) included

## 3 REVIEW RESULTS

### 3.1 SUMMARY OF DRUG USE DATA

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**Figure 1b. Nationally estimated number of bottles/packages of oral over-the-counter diphenhydramine-containing products, stratified by market category, sold from U.S. outpatient retail store outlets year 2011**

(b) (4)

### **3.2 FAERS CASES FOR DIPHENHYDRAMINE**

The FAERS search retrieved 12,538 total reports for all adverse events reported with DPH and DPH combination products. The top 5 preferred terms reported with DPH-containing products are: completed suicide, toxicity to various agents, overdose, intentional overdose, and drug ineffective.

Of the 12,538 cases, 4637 cases (36%) reported an outcome of death. The top 5 preferred terms reported with an outcome of death are: completed suicide, toxicity to various agents, cardiac arrest, death, and cardio-respiratory arrest.

This review will further describe FAERS cases related to accidents and intentional and unintentional overdose in the sections below.

### **3.3 ACCIDENTS**

#### **3.3.1 FAERS Cases of Accidents(n=37)**

The FAERS search retrieved 295 reports. After applying the case definition in Section 2.2.1 and accounting for duplicate reports, 37 cases were included in the case series of accidents reported with DPH use (see *Figure 1* in *Appendix E*).

*Table 5* summarizes the 37 FAERS cases of accidents reported with DPH for this case series.

*Appendix I* lists all the FAERS case numbers, FAERS version numbers, and manufacturer control numbers for the 37 cases in this case series.

<b>Table 5. Descriptive characteristics of Accidents reported with DPH use, received by FDA from (January 1, 1969 – July 10, 2013)</b>		
<b>(N=37)</b>		
Age (n= 31)	Mean	60 years
	Median	65 years
	Range	14 - 89 years
Sex	Male	17
	Female	19
	Unknown	1
Report year	2001	1
	2002	1
	2003	2
	2004	2
	2005	3
	2006	4
	2007	4
	2008	3
	2009	6
	2010	3
	2011	4
	2012	3
	2013	1
Report type	Expedited	33
	Direct	2
	Periodic	2
Serious Outcomes*	Death	2
	Life-threatening	1
	Hospitalized	7
	Other serious	28
Indication	None reported	5
	Accidental exposure	1
	Abuse	1
	Sleep aid	10
	Pain/insomnia	3
	Hypersensitivity	4
	Cold/congestion	8
	Allergies	4
	Shingles	1
Event Onset (time from last dose of DPH to event)	“Immediately”	1
	1 hour	1
	4 hours	1
	< 24 hours	27
	Unknown	7
Type of accident*	Fall	20
	MVA <sup>†</sup>	16
	Car	12
	Bus	2
	Unknown	2

	Reckless driving	2
	“Walked into door”	1
	“Cut arm”	1
Reported CNS <sup>*†</sup> Effect (n=28)	Drowsiness	8
	Disorientation	3
	Dizziness	4
	Memory loss	6
	Temporary loss of consciousness	10
	Confusion	2
	“Feeling high”	1
	“Not with it”	1

\*A report may have more than one outcome; type of accident; or reported CNS effect

†MVA= Motor Vehicle Accident; CNS = Central Nervous System

Of the 37 cases, 23 cases reported using a single ingredient DPH product. Six of the 23 single ingredient DPH cases reported using the DPH product as a sleep aid. The remaining 14 cases reported using the following multi-ingredient DPH products:

- containing 2 ingredients (n=9)
  - acetaminophen + DPH (n=6)
  - ibuprofen + DPH (n=2)
  - phenylephrine + DPH (n=1)
- containing 3 ingredients (n=5)
  - acetaminophen + DPH + phenylephrine (n=5)

Most cases (n=23) reported using DPH consistent with DPH labeling. More than half of the cases (n=17) reported using between 25 to 50 mg DPH (38 -76 mg for DPH citrate) once daily prior to the accident or injury. Five cases reported using between 75 to 300 mg in divided doses daily prior to the accident. One case reported using 6.25 mg DPH once.

Three of the 37 cases reported using doses greater than the labeled DPH dosing. One patient reported using 750 mg daily for months (case #3970755), and was involved in a minor motor vehicle accident. The second patient (case#4172909) reportedly took between 40 -120 50 mg capsules of Unisom SleepGels at one time, fell down the stairs, and sustained a head injury. The third patient (case#6908772) reportedly used 4 tablets of acetaminophen + DPH nightly at bedtime for 2 years. One day he fell asleep driving and caused a motor vehicle accident.

Nine cases did not report how much DPH was taken. In 2 cases, blood test results showed detectable levels of DPH.

Fifteen of the 37 cases reported injuries as a result of their accident. These cases ranged from non-serious injuries (e.g. “sore ribs and nose”) to serious injuries (e.g. bone fractures, head injuries, ruptured vertebrae). The two accident cases that resulted in death are summarized below.

### Fatal Cases (n=2)

#### FAERS case #3983279, 2003

A bus driver (unknown gender and age) was scheduled to drive an intercity bus from New York to Pittsburgh. The bus driver departed the right side of the roadway and struck the back of a parked tractor trailer. The bus driver and 6 passengers were killed; 16 bus passengers and 2 passengers in the tractor trailer were injured. Blood tests from the bus driver reported a DPH

level of 0.073 mcg/ml (therapeutic range not reported). The National Transportation Safety Board determined that the accident was caused, in part, by the use of DPH.

### FAERS case #6649818, 2008

A 43 year old female was involved in a car accident and died. The toxicology report (unknown date of testing) revealed a DPH level of 637 ng/ml (therapeutic range 30-300 ng/ml) in her blood. She had a history of bipolar disorder and her concomitant medications included duloxetine. No other information was reported.

### 3.3.2 Data Mining Results for Accidents

Table 6 lists data mining scores (EBGM values) and confidence limits for various MedDRA preferred terms (PT) previously described in the FAERS search strategy (Section 2.2.3) for DPH. Scores are sorted by EB05 value, i.e., the lower confidence limit of the EBGM value. This data mining analysis includes *all years* of AERS data (1969 through August 10, 2013).

<b>Table 6. Data Mining Scores for Accidents Query PTs Reported for DPH Products as of August 10, 2013. (All PTs and All Years of FAERS Data Searched)</b>				
<b>PT</b>	<b>N</b>	<b>EB05</b>	<b>EBGM</b>	<b>EB95</b>
Accident	61	4.8	5.9	7.3
Road traffic accident	43	1.1	1.5	1.9
Fall	111	0.7	0.8	0.9
Impaired driving ability	5	0.3	0.6	1.1
Injury	24	0.3	0.4	0.5
Accident at work	1	0.1	0.7	2.1

\*No reports were retrieved for the PT “Accident at home.”

It is noteworthy that none of the PTs in the “Accidents” query (Table 6) had an EB05 score  $\geq 2$  except for the PT “accident.”

## 3.4 ABUSE AND MISUSE

### 3.4.1 Summary of Literature

The search yielded two epidemiologic investigations relevant to this review, Sinyor et al., 2012<sup>7</sup>, and Jaffe et al., 2003<sup>8</sup>. Both studies were observational, cross-sectional investigations with no control groups, and reported descriptive data only.

- 1) Sinyor et al., 2012, looked at coroner data for completed overdose suicides in Toronto, Canada, between the years 1998 and 2007 to assess the frequency and psychological correlates of specific substances used in suicide. To identify implicated substances, data were obtained from the coroner’s toxicology and pathology reports. Details surrounding the suicide, including the mental health status of the decedent, were obtained through the coroner’s report via interviews with family, police, and physicians. Cases were abstracted if the coroner indicated “overdose” on the report as the official cause of intentional death.

Overall, 397 documented cases were used in the analysis. During this time period, opioid analgesics, sedative hypnotic or anxiolytic medications, OTC medications,

and tricyclic antidepressants represented the most frequently detected classes of drugs in lethal amounts (28.2%, 26.4%, 21.4%, and 20.4% of cases, respectively). DPH was the most common substance detected in lethal amounts among the cases, present in ~14% of all overdose suicides during that time period. This does not necessarily mean it was the only substance present at the time of death, only that it was at least one of the drugs present in lethal amounts. The proportion of suicides with DPH alone was not reported by the authors.

Several limitations were relevant to this study. First, the conclusions drawn by the coroner and pathologist could not be independently verified. Therefore, the veracity of their conclusions may be subject to bias due to misclassification of the cause of death, or inaccuracies regarding which substances were involved, particularly since multiple drugs were often present at the time of death. In addition, the relatively modest proportion of suicides involving illegal drugs (approximately 4%) may relate to coroner misclassification of an overdose death involving illegal drugs as unintentional instead of intentional. This differential misclassification happens when investigators believe that the consumption of illegal drugs is typically for intoxication and not deliberate harm. The authors conceded that this potential bias could have affected the findings that deemed DPH as the most common drug involved in Toronto's completed overdose suicides.

Another important note about this study is the lack of a control group, which precludes a formal assessment of the proportion of deaths that involved DPH. In addition, no statistical testing was undertaken to determine if this higher proportion was statistically significantly more than other substances.

- 2) Jaffe et al., 2004, surveyed admissions to two drug treatment facilities in the United Kingdom to illustrate the utility of using in-treatment drug and alcohol users for future post-market abuse liability studies. This specific study focused on 10 sedative-hypnotic drugs. The treatment centers where subjects were recruited serviced all types of abuse, but one center was primarily a detoxification facility for opioid abuse. The survey was conducted on 297 recent admissions to these pre-selected treatment centers, and a cluster analysis was performed to evaluate trends in subject responses related to specific sedative-hypnotic drugs. (A cluster analysis can detect whether there are related groupings of survey responses)

The drug categories included benzodiazepines, non-benzodiazepine hypnotics, antidepressants, and antihistamines (CPH and DPH). Survey questions included whether the subject had taken the drug, whether they used it medically at any point, and whether they had abused it. The abuse-related questions used proxy behaviors to identify abuse such as purchasing the drug on the street or using the drug to get high.

The results suggested a statistically significant cluster effect (related response grouping) for responses to survey questions targeting the abuse liability of the drugs. Of all the drugs in the survey, DPH (and CPH, the other antihistamine) showed the least amount of abuse potential relative to the other sedative-hypnotic drug categories. Approximately 11.6% of the subjects took DPH to "get high", 1.2% reported to be "addicted", and 8.1% felt they might become "addicted".

This study had several apparent limitations. First, there was uncertainty in the representativeness of the drug-abusing population surveyed. The authors did not describe why subjects were recruited from these specific centers or whether they

resemble all those who abuse drugs. There may also have been a temporal selection bias of subjects chosen since the authors chose to select only recent treatment admissions. Second, it is unclear whether the study findings' are generalizable to non-hardened drug using populations. If they are not, any understanding of the abuse liability of these drugs in the general population would be limited. Third, there are inherent biases associated with self-reporting as subjects may not actually know, or may misrepresent the truth about their use. Finally, similar to the Sinyor study, no control population or drug class was used in the inferential comparisons.

### 3.4.2 Summary of DAWN data

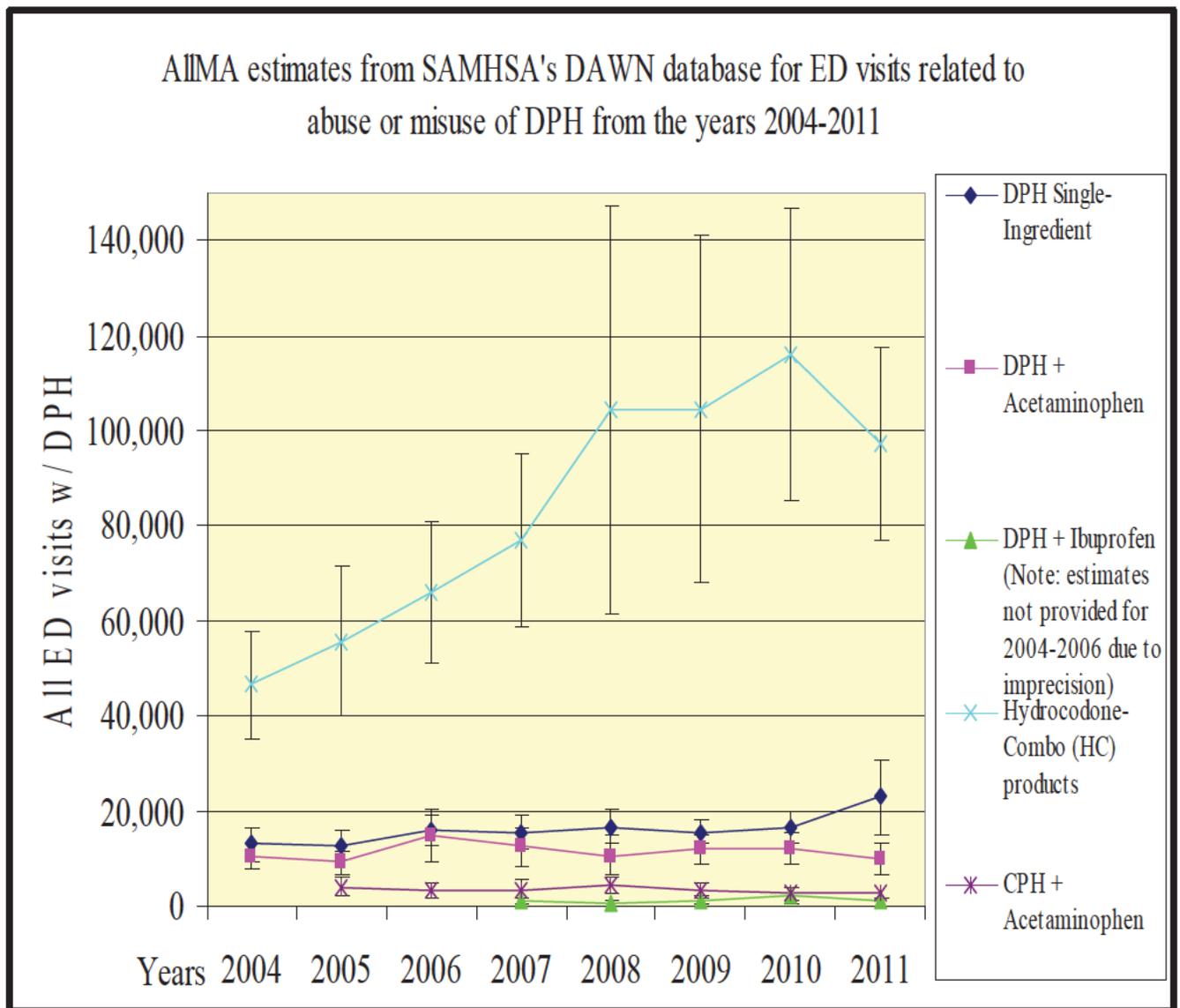
Figure 2 shows the temporal trend in the national estimates of All Misuse/Abuse (AllMA) ED visits associated with DPH (See Table 4 in Appendix F for numeric estimates).<sup>i</sup> Between 2004 and 2011, there was a 77% increase in the total number of DAWN AllMA ED visits associated with single-ingredient DPH, with estimates ranging from 12,962 in 2004 to 22,966 in 2011. Most of this increase occurred between 2010 and 2011.<sup>ii</sup> The increase was not as substantial when single-ingredient DPH was the only drug implicated in the visit [41%; 3,275 visits in 2004 to 5,569 in 2011 (see Table 4 in Appendix F)]. AllMA visits associated with DPH in combination with an analgesic remained relatively stable during that time period. Overall, a greater amount of AllMA ED visits are associated with single-ingredient DPH compared to DPH in combination with an analgesic substance. For comparison, ED visits are also provided for HC and CPH + acetaminophen. HC products with a known abuse liability ranged from 46,536 to 115,739 visits during that time period, while CPH + acetaminophen ranged from 3,376 to 4,478 visits (estimates could only be provided for 2005-2011). Single-ingredient CPH estimates could not be provided because the absolute numbers of ED visits were too small and/or there were high levels of imprecision in the estimates.

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<sup>i</sup> This includes DPH-containing products alone and in combination with other drugs

<sup>ii</sup> This could be artifactual and due to a greater amount of imprecision in the 2011 estimate as the confidence interval (CI) for the 2011 estimate is disproportionately larger than the CIs for other years. Typically we would include the next year's data to see if this upward trend continued and was not a result of imprecise estimates, but DAWN data collection ended in 2011.

Figure 2.



(\*\*\*Note: these estimates are for DPH alone and in combination with other drugs)

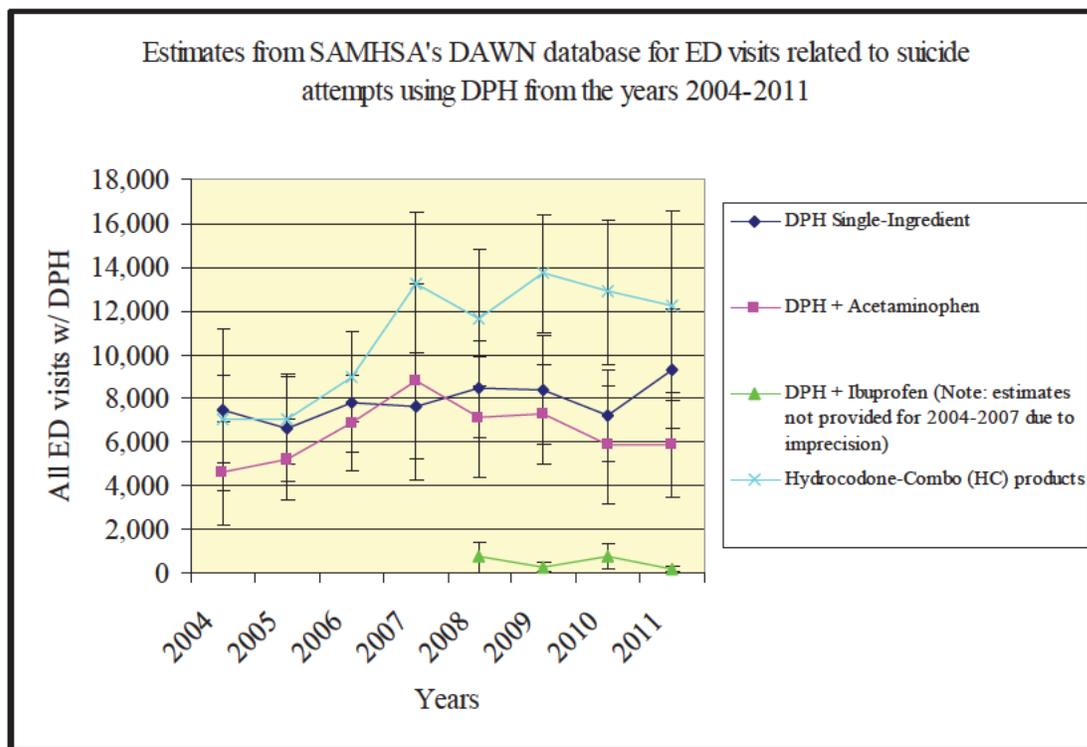
Figure 3 shows the temporal trend in suicide attempt (SA) ED visits associated with DPH (See Table 5 in Appendix F for numeric estimates).<sup>iii</sup> Overall DAWN SA ED estimates for single-ingredient DPH followed a less pronounced increasing trend than AllMA ED visits shown above, with a similar spike from 2010 to 2011.<sup>iv</sup> Between the years 2004 and 2011, SA visits increased

<sup>iii</sup> This includes DPH-containing products alone and in combination with other drugs

<sup>iv</sup> Again, this spike in 2011 could be due to greater imprecision in the 2011 estimate as the confidence interval (CI) for the estimate is disproportionately larger than the CIs for other years

by 25%, from 7,461 in 2004 to 9,301 in 2011. When single-ingredient DPH was the only drug implicated in the SA visit, estimates decreased by nearly 40% between 2004 (2,652 visits) and 2011 (1,597 visits) (See Table 5 in Appendix F). DPH in combination with an analgesic followed a similar overall trend to single-ingredient DPH between the years 2004 (4,581 visits) and 2011 (5,863), with DPH + acetaminophen increasing by 28%. However, the trend was not stable between 2004 and 2011 as the estimates ranged from 4,581 in 2004 to 8,755 in 2007 at its peak. Aside from 2007, single-ingredient DPH is associated with a greater amount of SA ED visits throughout this period than DPH in combination with an analgesic substance. For comparison, HC products ranged from 7,034 to 13,701 during that time period. CPH + acetaminophen had only one reportable estimate, 2007, where there were 684 visits, and no estimates for single-ingredient CPH could be provided.

Figure 3.



(\*\*\*Note: these estimates are for HC and DPH alone and in combination with other drugs)

There were 1,098 *reportable*<sup>v</sup> deaths associated with DPH in the 13 states covered by DAWN reported by coroners and medical examiners between 2004 and 2011 (See Tables 6 & 7 in Appendix F for all counts). These deaths were classified as misuse/abuse, homicide, accidental poisoning, adverse reactions, or unknown. Individual state totals varied considerably. Five states (MA, MD, NM, OK, and UT) had a sufficient number of deaths for reporting in at least seven of the eight years included. Of those states, the data for MD and UT indicate a possible decline, and OK and NM a possible increase; however, differences in methodology and classification could

<sup>v</sup> These “reportable” deaths would not include suppressed death counts in states where there were too few deaths to report and maintain confidentiality

account for these findings. The other states did not show any type of apparent pattern. When the deaths were restricted to suicides, only four states (MA, MD, NM, and UT) had sufficient numbers for reporting in the majority of the time period examined. The counts ranged from zero to 16, and no temporal trends were apparent.

### 3.4.3 DAWN (AllMA) Ratios

(b) (4)



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<sup>vi</sup> Although an increase in ED visits associated with DPH could also cause an increase in the ratio, this dramatic change in 2011 could be driven largely by a decrease in sales.

*Table 8* shows a comparable pattern of ratios to those in *Table 7*. After adjusting for its utilization, single-ingredient DPH typically accounts for less SA ED visits than DPH + acetaminophen despite higher amounts sales between 2007 and 2011. A similar uptick in SA ratios for 2011 is observed and could also be due to the possible effects of recalls.<sup>vii</sup>

(b) (4)

#### **3.4.4 FAERS Cases of Intentional Overdose (n=4401)**

The FAERS search retrieved 4467 cases coded with the preferred terms drug abuse, intentional drug misuse, intentional overdose, overdose, completed suicide, or toxicity to various agents (these PTs are referred to as intentional overdose in this review) and DPH as a suspect product. Of the 4467 cases, 66 cases are also coded with the preferred term accidental overdose. These cases were excluded from the intentional overdose case series and are described in section 3.4.7. (unintentional overdose). After excluding 66 cases for accidental overdose, 4401 cases were included in the case series of intentional overdose reported with DPH as a suspect product. These are crude counts and the cases were not de-duplicated or assessed for an association between DPH and intentional overdose.

*Table 9* in *Appendix G* summarizes the 4401 FAERS cases of intentional overdose reported with DPH for this case series.

Of the 4401 cases, 2231 cases list a DPH containing product as the primary suspect medication. The 2231 cases list DPH as:

- a single ingredient product (n=1338)

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<sup>vii</sup> *ibid*

- containing 2 ingredients (n=887)
  - acetaminophen + DPH (n=785)
  - ibuprofen + DPH (n=87)
  - DPH + phenylephrine (n=10)
  - DPH + pseudoephedrine (n=3)
- containing 3 or more ingredients (n=6)
  - acetaminophen + DPH + pseudoephedrine (n=3)
  - acetaminophen + dextromethorphan + DPH + pseudoephedrine (n=2)
  - acetaminophen + chlorpheniramine + dextromethorphan + DPH + doxylamine + pseudoephedrine (n=1).

Most cases (n=3511) report the patient was using multiple medications and/or recreational drugs at the time of the event; 890 cases (20%) report the patient as using only a DPH containing product at the time of the event.

Of the 4401 cases, 69% (3047/4401) appeared in published literature. Most of these cases (2595/4401) were published in the Annual Report of American Association of Poison Control Centers National Poison Data System (AAPCC-NPDS).

Three-fourths of the cases reported an outcome of death (3315/4401). Most cases did not provide an indication for DPH use; however, 597 cases did indicate abuse and 120 cases indicated DPH was used as a sleep aid.

Most cases (4204/4401) were reported between the year 2000 and 2013. Of note, 71% (3133/4401) were reported between December 22, 2007<sup>viii</sup> and July 10, 2013.

### 3.4.5 Summary of NEISS-CADES data

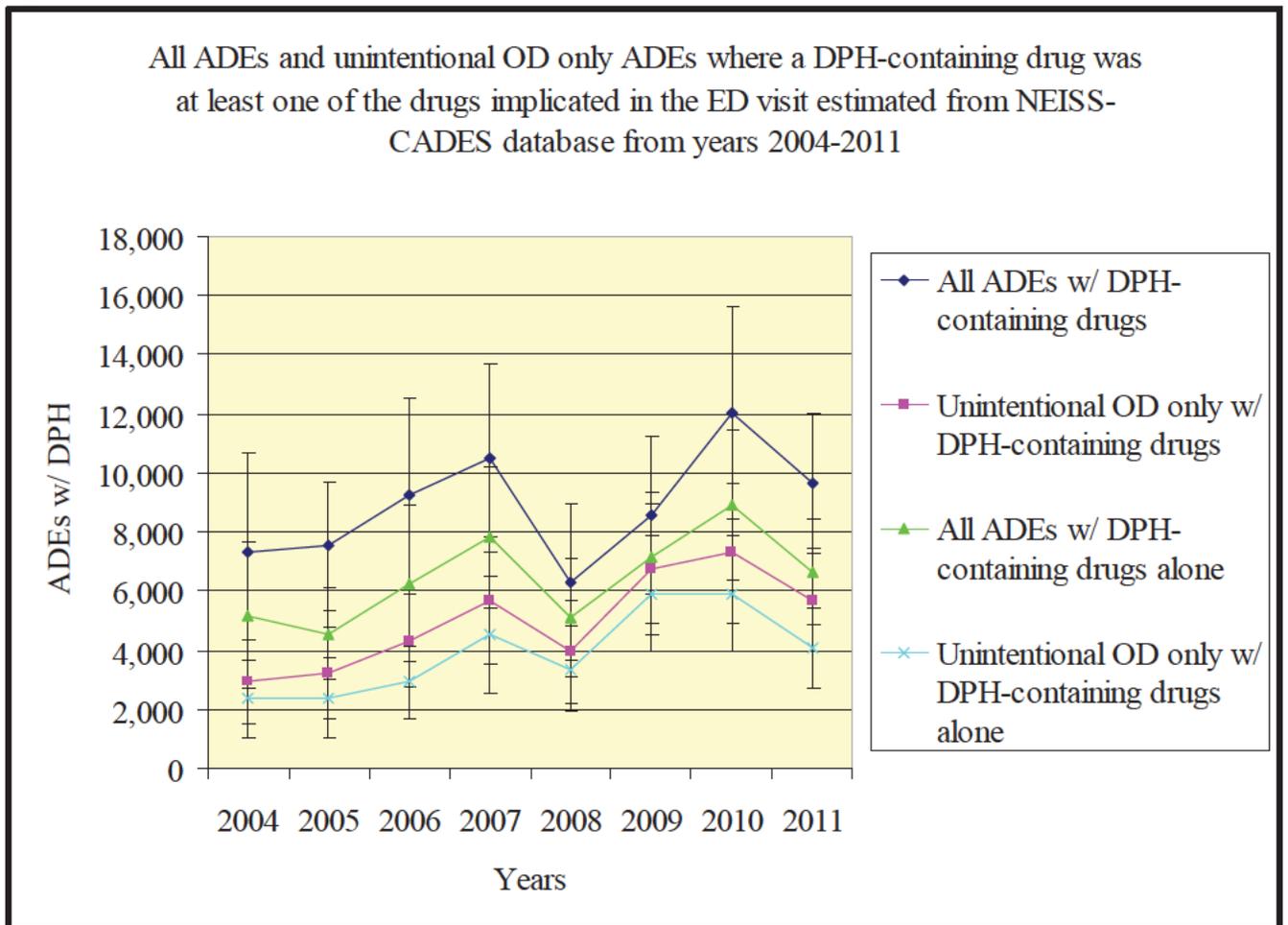
*Figure 4* shows the temporal trend in the national estimates of ADEs associated with DPH that resulted in an ED visit (*See Table 8 in Appendix F for numeric estimates*). From the years 2004 (7,340 ED visits) to 2011 (9,640 ED visits), there was a 31% increase in all ADEs. It is not clear why there was a large decrease in ED visits in 2008.<sup>ix</sup> When unintentional ODs associated with DPH were separated out from all ADEs, the increase was more pronounced between 2004 and 2011 (93%; 2,950 visits in 2004 to 5,685 in 2011). The average percentage of all ADEs that were specifically categorized as unintentional ODs was 56% during the entire time period. When only DPH-containing drugs were implicated in the ADE or unintentional OD, similar trends were observed.

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<sup>viii</sup> Date Public Law 109-462 became effective, which required manufacturers to submit expedited 15 day reports for the monograph products

<sup>ix</sup> This may be spurious and due to methodological changes in data collection

Figure 4.



### 3.4.6 NEISS-CADES (ADE) Ratios

Table 9 shows ADEs for DPH-containing drugs relative to sales of all drugs containing DPH [ADE Ratio (ADR)]. ADRs remained relatively stable over this time period. The decrease in overall sales in 2011 did not affect ADRs as markedly as ARs.

### 3.4.7 FAERS Cases of Unintentional Overdose (n=268)

The FAERS search retrieved 268 cases coded with the preferred term accidental overdose and DPH as a suspect product. These are crude counts and cases were not de-duplicated or assessed for an association between DPH and unintentional overdose.

*Table 10* in *Appendix H* summarizes the 268 FAERS cases of accidental overdose reported with DPH for this case series.

Of the 268 cases, 104 cases list a DPH containing product as the primary suspect medication. The 104 cases list DPH as:

- a single ingredient product (n=74)
- containing 2 ingredients (n=29)
  - acetaminophen + DPH (n=16)
  - ibuprofen + DPH (n=9)
  - acetaminophen + phenylephrine (n=3)
  - phenylephrine + DPH (n=1)
- containing 3 ingredients (n=1)
  - acetaminophen + DPH + pseudoephedrine (n=1)

Most cases (n=189) report the patient was using multiple medications at the time of the event; 79 cases (30%) report the patient as using only a DPH containing product at the time of the event.

### 3.4.8 Data Mining of FAERS Cases of Intentional and Unintentional Overdose

Tables 10 and 11 list data mining scores (EBGM values) and confidence limits for various MedDRA preferred terms (PT) previously described in the FAERS search strategy (Section 2.3.6)

for DPH. Scores are sorted by EB05 value, i.e., the lower confidence limit of the EBGM value. This data mining analysis includes *all years* of AERS data (1969 through August 10, 2013).

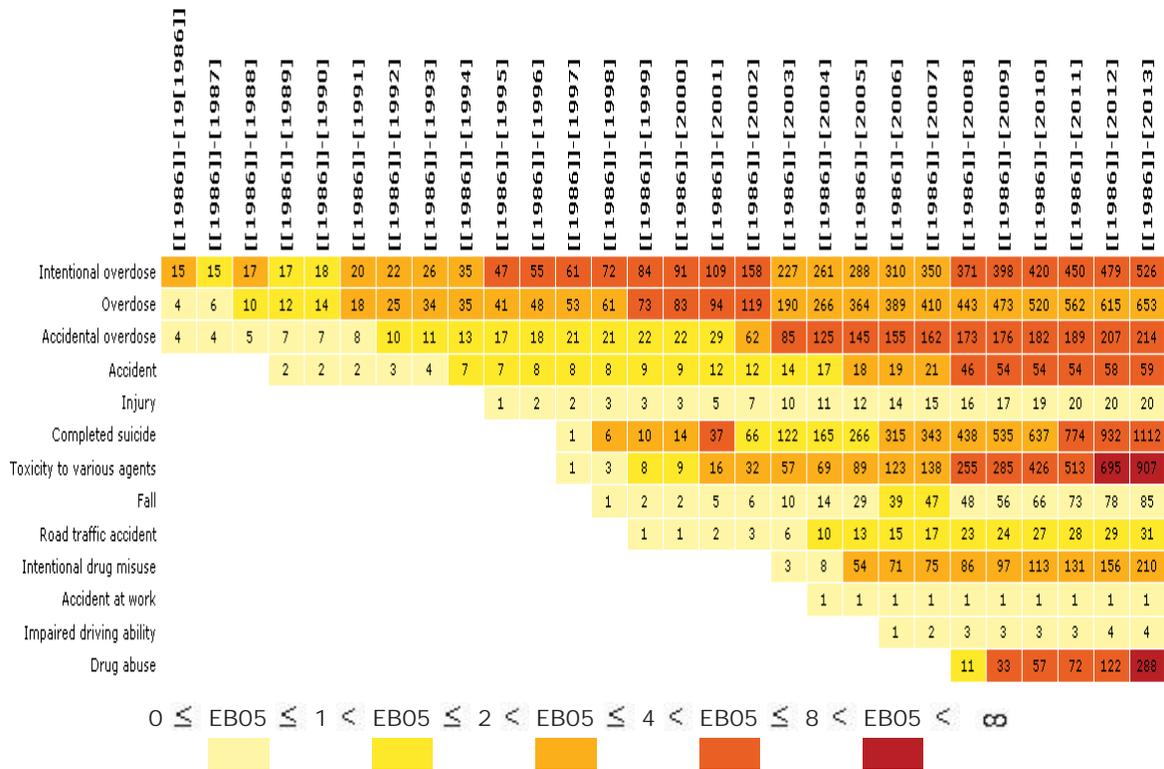
<b>Table 10. Data Mining Scores for Intentional Overdose Query PTs Reported for DPH Products as of August 10, 2013. (All PTs and All Years of FAERS Data Searched)</b>				
<b>PT</b>	<b>N</b>	<b>EB05</b>	<b>EBGM</b>	<b>EB95</b>
Toxicity to various agents	1295	11.5	12.1	12.6
Drug abuse	311	8.7	9.6	10.5
Completed suicide	1548	6.9	7.2	7.5
Intentional overdose	741	6.0	6.4	6.8
Intentional drug misuse	336	4.5	4.9	5.4
Overdose	845	4.0	4.3	4.5

<b>Table 11. Data Mining Scores for Unintentional Overdose Query PTs Reported for DPH Products as of August 10, 2013. (All PTs and All Years of FAERS Data Searched)</b>				
<b>PT</b>	<b>N</b>	<b>EB05</b>	<b>EBGM</b>	<b>EB95</b>
Accidental overdose	245	5.3	5.9	6.5

As is noted in the above tables, the highest data mining score (EBGM = 12.1) is for the PT “toxicity to various agents.”

Figure 5 below displays data mining scores by year for DPH as a generic name (i.e., combination products containing DPH excluded) in FAERS. For further information regarding data mining scores and their interpretation, see *Appendix B* and also the Discussion section.

**Figure 5. Cumulative Data Mining Scores and Cumulative Cases for DPH by Year, Generic (S) 10498 Run for Selected Overdose and Accidents PTs, All Years of FAERS data.**



#### 4 DISCUSSION

This review shows that DPH-containing products are associated with accidents, misuse/abuse, suicide attempts, and unintentional ODs, however, the frequencies of these events are relatively modest given its wide OTC utilization. In addition, the current and proposed labeling for DPH sleep aid products describes the CNS effects of DPH and provides cautions regarding driving or operating machinery with these products.



(b) (4)

Compared to widespread use of DPH and years on the market, the FAERS accident case series had relatively few cases (n=37). In addition, data mining scores for the PTs in the accident case series all had EB05 values  $\leq 2$  with one exception. The PT “accident” had an EBO5 of 4.8 which indicated a potential signal. The potential for increased risk of accidents while using DPH is plausible due to the CNS impairment from DPH. However, after review of the accident cases, there were relatively few FAERS cases included in this case series. Of the 37 included cases, 18 cases reported accidents related to motor vehicle accidents and 20 cases reported injuries as result of a fall. Injuries in these cases ranged from non-serious injuries (e.g., “sore ribs and nose”) to serious injuries (e.g., bone fractures, head injuries, ruptured vertebrae). This case series reported the fewest cases of death (n=2). One of these cases involved a bus accident where the driver and 6 passengers were killed.

The literature review did not show a consistent association between DPH and abuse or suicidality. A search of the literature yielded only two relevant observational studies regarding the association between DPH-containing products, and misuse/abuse or suicidality. Sinyor et al, 2012, found that DPH was the most prevalent drug detected in lethal amounts post-mortem in suspected suicides in Toronto, Canada from 1998 to 2007. However, the small number of deaths, lack of independent verification, and possible coroner bias in judging intentionality render these results suspect. Despite these biases, the relatively high proportion of completed suicides associated with DPH in this Canadian population is germane to the issue of postmarketing safety of DPH in the U.S., particularly in light of DPH being an OTC product with widespread availability. Ultimately, this study showed that DPH is a commonly used agent in suicides in Canada. Although it is unknown how much this directly relates to the U.S. population, one can infer that DPH is used in some completed suicides, and that the frequency was comparable to other drugs used in completed suicides in Toronto during that time period.

The other study, by Jaffe et al, 2004, showed a clustering of answers to targeted abuse liability questions to drug users admitted to drug treatment centers in the U.K. The drugs of interest were sedative/hypnotic drugs. Of all the drugs that were a part of the survey, the antihistamines (of which DPH was one of two) showed the lowest abuse liability compared to the other drugs. This study had several issues including the generalizability of the study population, and a potential for selection bias. From an epidemiological standpoint, the results are limited in the inferences that can be made in regard to DPH, however, one can infer that among this sample of inpatient drug users, DPH had a low amount of self-reported abuse potential relative to the other surveyed drugs in that class.

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<sup>x</sup> Source: OTC International Market Tracking (OTCIMS). Years 2007-2012. Data extracted September 2013.

From the total DPH FAERS data, death was reported as an outcome in 36% (4637/12538) of the cases, which was lower than the percentage of fatal cases (43.9%, 2476/5644) found in Bayer's review of the publicly available FAERS data. The difference in total number of cases between Bayer's FAERS data and actual FAERS data may be due to how products are coded in FAERS, and the search strategies that DPV utilized versus the Bayer search strategy.

A majority of FAERS cases that reported an outcome of death with DPH use were reported in the intentional overdose case series (71%, 3315/4637). Consistent with the drug utilization data, the multi-ingredient pain/sleep aid DPH products (i.e., acetaminophen + DPH or ibuprofen + DPH) were reported in less than half of the total DPH cases.

Although it is difficult to determine from the FAERS cases the reasons why DPH is abused, DPH was reported as the only medication on board at the time of event in less than half of the cases. The majority of cases (80% of cases in the intentional overdose case series and 70% of cases in the unintentional overdose case series) reported using or abusing multiple medications or recreational substances (including alcohol) along with DPH. DPH may be desirable since there is unrestricted access to OTC DPH and it can be found in many people's homes.

Data mining scores (EBGM values and accompanying EB05, EB95 confidence limits) were generally consistent with what is known about DPH. For the overdose PTs queried, all had EB05 values  $\geq 2$ . When considering data mining score trends by year (*Figure 5*), we noted increasing data mining scores for several PTs over the past few years, especially for the PTs "drug abuse" and "toxicity to various agents." These data mining results are consistent with the FAERS results for intentional overdose case series. Seventy-one percent (3133/4401) of cases were reported between December 22, 2007 and July 10, 2013, for this case series. This increased trend of data mining scores and FAERS case may be related to Public Law 109-462, which required manufacturers to submit expedited 15 day reports for the monograph products.

The All Misuse/Abuse (AllMA) DAWN data showed that overall, single-ingredient DPH has had relatively steady increases in ED visits over this time period, while DPH + acetaminophen ED visits have remained consistent. DPH had markedly fewer ED visits associated with it than HC, but more than CPH + acetaminophen. DAWN ED visit estimates related to suicide attempts (SAs), showed increasing trends for both single-ingredient DPH and DPH + acetaminophen. DAWN data suggest that 1.4% of all AllMA ED visit estimates were associated with DPH, and 7.6% of all suicide attempt ED visits were associated with DPH. Due to low numbers of unintentional deaths and suicides in the SAMHSA data resource, these data could not materially contribute to this assessment.

(b) (4)



(b) (4)



There are some limitations to this assessment. The DAWN data and NEISS-CADES data were not tested for statistical significance. All figures, other than state-specific death data, are national estimates based on applied sampling weights. DAWN data and NEISS-CADES data are subject to misclassification of the event of interest and the drugs involved. The DAWN AllMA construct used is a broad category that includes various explanations on why a patient presented at an ED. It is meant to provide an approximation of abuse and misuse, but is not specific to those categories. DAWN death data only cover 13 states, and due to DAWN criteria, the reported drug is a contributing factor but may not be the direct cause of death. DAWN also ceased data collection at the end of 2011, and the spike in ED visits related to DPH during 2011 could not be compared to subsequent years. The unintentional OD category in NEISS-CADES is not, in principle, meant to include instances of confirmed misuse or abuse, but due to misclassification of these, particularly with OTC products that may have a relatively low perceived abuse liability, the totality of data (DAWN and NEISS-CADES) is meant to ensure that most of the misuse or abuse-related events are accounted in this assessment. In addition, since the majority of DPH products are regulated under the monograph, reporting of serious adverse events was not required by manufacturers of monographs until Public Law 109-462 became effective on December 22, 2007. Due to this Law, there has been an increase in reporting for the monograph products, which may affect the increase in FAERS cases seen in recent years.

## 5 CONCLUSION

This review shows that DPH-containing products are associated with accidents, misuse/abuse, suicide attempts, and unintentional overdoses; however, the frequencies of these events are relatively modest given its wide OTC utilization. In addition, the current and proposed labeling for DPH sleep aid products describes the CNS effects of DPH and provides cautions regarding driving or operating machinery with these products.

Despite the limitations of this assessment, the DAWN data and NEISS-CADES data show roughly stable rates with a marginally increasing trend of ED visits over the given time period. However, how much a new DPH-containing product will contribute to an increase in ED visits cannot be directly inferred from the data. The introduction of this product would likely result in similar levels of abuse/misuse, and accidents/injuries seen with other DPH analgesic combination products. The potential for abuse/misuse and suicide attempts with this product exists, but the data do not suggest that the risk of these events is similar to drugs with a known potential for abuse/misuse (e.g., hydrocodone-combination products), or that it will be disproportionate, given its widespread availability.

## 6 RECOMMENDATIONS

This review did not identify any new safety issues with diphenhydramine hydrochloride. OSE agrees with the proposed labeling for CNS effects and effects on driving submitted with NDA 205352 (naproxen sodium + diphenhydramine hydrochloride).

## 7 REFERENCES

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## 8 APPENDIX

### 8.1 APPENDIX A. DRUG UTILIZATION DATABASE DESCRIPTIONS

#### *OTC International Market Tracking (OTCIMS)*

The OTC International Market Tracking (OTCIMS) platform can provide the FDA with highly accurate retail sales data for all OTC drugs. OTCIMS tracks key molecular data characteristics, strength of active ingredients; dosage form; and size of drug products by mL, number of tablets/ capsules, and/or total doses available. OTCIMS data is delivered quarterly in CD format and accessible through a secure, stand-alone desktop application called Dataview™.

The findings should be interpreted in the context of the known limitations of OTCIMS. The OTCIMS database tracks retail sales data and captures approximately 70% of sales activity of OTC products from retail drug stores, food stores, and mass merchandisers (excluding Wal-Mart) – retail sales data are projected to represent U.S. retailer universe. The OTCIMS database does not provide information of the individual purchaser, the intended user, or the patient's actual usage/consumption of OTC products; as a result, a reliable estimate of direct patient use of OTC products is not possible. Moreover, the analyses only focused on the outpatient retail settings, therefore these estimates may not apply to other settings of care such as online purchasing. Due to these limitations, not all of the retail sales or the household purchasing data of oral OTC DPH-containing products in the U.S. is captured in this analysis, and the true extent of use of oral OTC DPH-containing products is at best underestimated.

The estimates provided are national estimates, but no statistical tests were performed to determine statistically significant changes over time or between products. Therefore, all changes over time or between products should be considered approximate, and may be due to random error.

## **8.2 APPENDIX B. DESCRIPTION OF FAERS AND EMPIRICA SIGNAL**

### **FDA Adverse Event Reporting System (FAERS)**

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FDA implemented FAERS on September 10, 2012, and migrated all the data from the previous reporting system (AERS) to FAERS. Differences may exist when comparing case counts in AERS and FAERS. FDA validated and recoded product information as the AERS reports were migrated to FAERS. In addition, FDA implemented new search functionality based on the date FDA initially received the case to more accurately portray the follow up cases that have multiple receive dates.

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

### **Data Mining of FAERS using Empirica Signal**

Empirica Signal refers to the software that OSE uses to perform data mining analyses while using the Multi-item Gamma Poisson Shrinker (MGPS) data mining algorithm. "Data mining" refers to the use of computer algorithms to identify patterns of associations or unexpected occurrences (i.e., "potential signals") in large databases. These potential signals can then be evaluated for intervention as appropriate. In OSE, the FDA Adverse Event Reporting System (FAERS) database is utilized for data mining. MGPS analyzes the records in FAERS and then quantifies reported drug-event associations by producing a set of values or scores that indicate varying strengths of reporting relationships between drugs and events. These scores, denoted as Empirical Bayes Geometric Mean (EBGM) values, provide a stable estimate of the relative reporting of an event for a particular drug relative to all other drugs and events in FAERS. MGPS also calculates lower and upper 90% confidence limits for EBGM values, denoted EB05 and EB95, respectively. Because EBGM scores are based on FAERS data, limitations relating to FAERS data also apply to data mining-derived data. Further, drug and event causality cannot be inferred from EBGM scores.

### 8.3 APPENDIX C. DAWN ANALYSIS DATA REQUEST

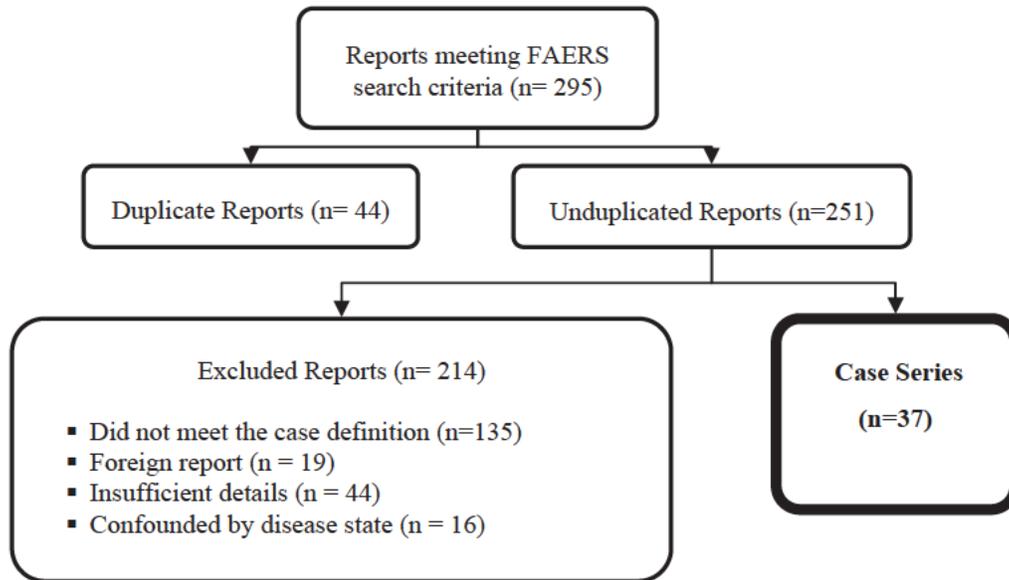
**Table 1. DAWN analysis data request**

<i>Drug ID</i>	<i>Drugs of interest</i>	<i>Category</i>
d03445	acetaminophen-diphenhydramine	CNS AGENTS
d05495	acetaminophen/dextromethorphan/diphenhydramine	RESPIRATORY AGENTS
d07517	acetaminophen/dextromethorphan/diphenhydramine/PE	RESPIRATORY AGENTS
d04165	acetaminophen/dextromethorphan/diphenhydramine/PSE	RESPIRATORY AGENTS
d05654	acetaminophen/diphenhydramine/phenylephrine	RESPIRATORY AGENTS
d04168	acetaminophen/diphenhydramine/pseudoephedrine	RESPIRATORY AGENTS
d03329	ASA/diphenhydramine/PPA	RESPIRATORY AGENTS
d04155	aspirin-diphenhydramine	CNS AGENTS
d03575	bromodiphenhydramine	RESPIRATORY AGENTS
d03576	bromodiphenhydramine-codeine	RESPIRATORY AGENTS
d07064	brompheniramine/diphenhydramine/phenylephrine	RESPIRATORY AGENTS
d07063	brompheniramine-diphenhydramine	RESPIRATORY AGENTS
d04895	carbetapentane/diphenhydramine/phenylephrine	RESPIRATORY AGENTS
d05875	carbetapentane-diphenhydramine	RESPIRATORY AGENTS
d07367	codeine/diphenhydramine/phenylephrine	RESPIRATORY AGENTS
d05877	dextromethorphan/diphenhydramine/PE	RESPIRATORY AGENTS
d00212	diphenhydramine	CNS AGENTS
d04925	diphenhydramine/hydrocodone/phenylephrine	RESPIRATORY AGENTS
d07469	diphenhydramine-guaifenesin	RESPIRATORY AGENTS
d05819	diphenhydramine-ibuprofen	CNS AGENTS
d04175	diphenhydramine-magnesium salicylate	CNS AGENTS
d04861	diphenhydramine-phenylephrine	RESPIRATORY AGENTS
d03312	diphenhydramine-pseudoephedrine	RESPIRATORY AGENTS

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## 8.5 APPENDIX E. FAERS SELECTION OF ACCIDENTS CASE SERIES

Figure 1.



## 8.6 APPENDIX F. DAWN AND NEISS-CADES DATABASE RESULTS

Table 4. AllMA estimates from SAMHSA's DAWN database for ED visits related to abuse or misuse of DPH from the years 2004-2011.

Drug class (as categorized in DAWN)	Drug formulation	Estimate category	2004 Estimate (95% CI)	2005 Estimate (95% CI)	2006 Estimate (95% CI)	2007 Estimate (95% CI)	2008 Estimate (95% CI)	2009 Estimate (95% CI)	2010 Estimate (95% CI)	2011 Estimate (95% CI)
All drugs in DAWN database		All ED visits in DAWN database	1,619,056 (1,134,972 – 2,103,141)	1,616,404 (1,329,184 – 1,903,625)	1,742,942 (1,451,092 – 2,034,792)	1,883,280 (1,561,498 – 2,205,062)	1,999,877 (1,692,936 – 2,306,818)	2,070,452 (1,779,197 – 2,361,707)	2,301,050 (1,987,721 – 2,614,380)	2,462,948 (2,112,868 – 2,813,028)
CNS Agent- Misc.	DPH single- ingredient	All visits w/ DPH	12,962 (9,230 – 16,693)	12,909 (10,155 – 15,663)	15,921 (12,764 – 19,077)	15,627 (12,192 – 19,061)	16,689 (13,032 – 20,346)	15,626 (12,917 – 18,335)	16,485 (13,131 – 19,839)	22,966 (15,073 – 30,860)
		DPH as only drug implicated	3,275 (1,307 – 5,243)	3,412 (1,957 – 4,866)	4,531 (3,086 – 5,975)	3,808 (2,124 – 5,493)	5,134 (3,456 – 6,813)	4,559 (3,387 – 5,731)	4,670 (3,187 – 6,153)	5,569 (2,872 – 8,266)
		DPH w/ Alcohol	5,038 (3,696 – 6,380)	5,319 (3,796 – 6,842)	6,327 (4,453 – 8,201)	5,716 (3,601 – 7,831)	5,149 (3,639 – 6,658)	4,423 (3,260 – 5,586)	3,977 (2,725 – 5,229)	7,672 (3,872 – 11,472)
CNS Agent- Analgesic combo	DPH + acetaminophe n	All visits w/ DPH	10,238 (7,426 – 13,051)	9,102 (6,477 – 11,727)	14,887 (9,188 – 20,586)	12,427 (8,296 – 16,558)	10,651 (6,732 – 14,571)	11,850 (8,940 – 14,759)	12,205 (9,006 – 15,405)	9,707 (6,489 – 12,925)
	DPH + Ibuprofen	All visits w/ DPH	*	*	*	865 (146 – 1,584)	629 (263 – 995)	1,225 (435 – 2,014)	2,224 (480 – 3,968)	1,013 (256 – 1,770)

\* = Estimates cannot be provided due to imprecision

Table 5. Estimates from SAMHSA's DAWN database for ED visits related to suicide attempts using DPH from the years 2004-2011

Drug class (as categorized in DAWN)	Drug formulation	Estimate category	2004 Estimate (95% CI)	2005 Estimate (95% CI)	2006 Estimate (95% CI)	2007 Estimate (95% CI)	2008 Estimate (95% CI)	2009 Estimate (95% CI)	2010 Estimate (95% CI)	2011 Estimate (95% CI)
All drugs in DAWN database		All ED visits in DAWN database	161,586 (130,829 – 192,343)	151,568 (127,715 – 175,421)	182,805 (154,185 – 211,424)	197,053 (164,564 – 229,542)	199,469 (173,141 – 225,797)	198,403 (166,539 – 230,268)	212,736 (170,532 – 254,940)	228,366 (197,745 – 258,986)
CNS Agent– Misc.	DPH single ingredient	All visits w/ DPH	7,461 (3,800 – 11,123)	6,583 (4,200 – 8,967)	7,760 (5,547 – 9,974)	7,620 (5,223 – 10,017)	8,414 (6,219 – 10,610)	8,384 (5,861 – 10,907)	7,195 (5,087 – 9,302)	9,301 (6,587 – 12,014)
		DPH as only drug implicated	2,652 (1,164 – 4,139)	2,191 (1,044 – 3,338)	1,483 (718 – 2,249)	1,315 (605 – 2,025)	2,490 (1,256 – 3,725)	2,128 (983 – 3,272)	1,555 (841 – 2,268)	1,597 (773 – 2,421)
		DPH w/ Alcohol	1,419 (487 – 2,350)	1,594 (889 – 2,298)	2,968 (1,482 – 4,453)	2,391 (1,273 – 3,509)	2,166 (1,175 – 3,157)	1,976 (993 – 2,959)	1,212 (699 – 1,726)	3,027 (314 – 5,739)
CNS Agent– Analgesic combo	DPH + acetaminophen	All visits w/ DPH	4,581 (2,218 – 6,943)	5,190 (3,333 – 7,048)	6,872 (4,668 – 9,075)	8,755 (4,245 – 13,266)	7,118 (4,337 – 9,898)	7,246 (4,971 – 9,521)	5,829 (3,158 – 8,499)	5,863 (3,416 – 8,310)
	DPH + Ibuprofen	All visits w/ DPH	*	*	*	*	735 (36 – 1,434)	291 (91 – 492)	752 (173 – 1,331)	207 (83 – 331)

\* = Estimates cannot be provided due to imprecision

Table 6. Number of deaths (excluding suicide) associated with DPH as reported in medical examiner or coroner reports from SAMHSA's DAWN database for years 2004-2010

State	2004	2005	2006	2007	2008	2009	2010
DE	N/A	N/A	N/A	N/A	N/A	4	*
MA	N/A	6	23	18	20	19	23
MD	50	35	23	36	18	20	18
ME	*	*	*	6	10	6	7
NH	*	*	*	*	*	*	*
NM	4	4	*	13	15	19	19
OK	N/A	7	11	15	22	15	29
OR	N/A	N/A	N/A	30	23	4	7
RI	N/A	N/A	N/A	N/A	8	4	4
UT	42	51	39	69	42	36	33
VA	N/A	N/A	N/A	19	11	27	38
VT	*	*	*	*	*	*	4
WV	N/A	N/A	N/A	N/A	26	37	29

*N/A = Information was not collect during that time period*  
*\* = Number is suppressed for confidentiality*  
**NOTE** *DPH may have been in combination with other substances*

Table 7. Number of suicides associated with DPH as reported in medical examiner or coroner reports from SAMHSA's DAWN database for years 2004-2010

State	2004	2005	2006	2007	2008	2009	2010
DE	N/A	N/A	N/A	N/A	N/A	*	*
MA	N/A	6	10	12	8	12	8
MD	9	10	10	9	7	11	16
ME	4	*	*	*	4	5	4
NH	*	*	*	4	*	*	5
NM	0	4	*	4	7	6	6
OK	N/A	*	6	7	6	4	*
OR	N/A	N/A	N/A	7	12	10	*
RI	N/A	N/A	N/A	N/A	*	5	*
UT	13	12	15	10	10	13	7
VA	N/A	N/A	N/A	11	18	18	17
VT	0	*	*	*	*	0	5
WV	N/A	N/A	N/A	N/A	6	6	*

*N/A = Information was not collect during that time period*  
*\* = Number is suppressed for confidentiality*  
**NOTE** *DPH may have been in combination with other substances*

Table 8. All ADEs associated with DPH and unintentional OD only ADEs estimated from the NEISS-CADES database from years 2004-2011

ADE type	2004 Estimate (95% CI)	2005 Estimate (95% CI)	2006 Estimate (95% CI)	2007 Estimate (95% CI)	2008 Estimate (95% CI)	2009 Estimate (95% CI)	2010 Estimate (95% CI)	2011 Estimate (95% CI)
All ADEs w/ DPH-containing drug	7,340 (3,996 – 10,684)	7,537 (5,350 – 9,724)	9,246 (5,921 – 12,571)	10,507 (7,314 – 13,700)	6,307 (3,665 – 8,949)	8,589 (5,929 – 11,248)	12,040 (8,456 – 15,624)	9,640 (7,257 – 12,022)
Unintentional OD only w/ DPH- containing drug	2,950 (1,517 – 4,383)	3,232 (1,719 – 4,745)	4,341 (2,803 – 5,879)	5,683 (3,510 – 7,857)	3,956 (2,208 – 5,704)	6,760 (4,549 – 8,972)	7,315 (4,954 – 9,676)	5,685 (3,952 – 7,420)
All ADEs <u>involving</u> DPH- containing drug alone	5,181 (2,706 – 7,656)	4,561 (2,986 – 6,135)	6,256 (3,608 – 8,903)	7,841 (5,478 – 10,204)	5,128 (3,130 – 7,126)	7,152 (4,914 – 9,391)	8,919 (6,387 – 11,451)	6,662 (4,866 – 8,459)
Unintentional OD only <u>involving</u> DPH-containing drug alone	2,366 (1,028 – 3,705)	2,409 (1,043 – 3,774)	2,933 (1,709 – 4,157)	4,542 (2,577 – 6,506)	3,368 (1,913 – 4,823)	5,926 (3,974 – 7,879)	5,929 (3,962 – 7,895)	4,097 (2,746 – 5,449)

**8.7 APPENDIX G. DESCRIPTIVE CHARACTERISTICS OF FAERS CASES OF INTENTIONAL OVERDOSE REPORTED WITH DPH USE (N=4401)**

<b>Table 9. Descriptive characteristics of Intentional Overdose reported with DPH use, received by FDA from (January 1, 1969 – July 10, 2013) (N=4401)<sup>†</sup></b>		
Age (n=3942)	Mean	39 years
	Median	39 years
	Range	1 day - 97 years
	≤17 years	9% (n = 347)
Sex	Male	1506
	Female	2423
	Unknown	472
Report year	1969-1979	11
	1980-1989	15
	1990-1999	171
	2000-2009	1768
	2010-2013	2436
Reports from 12/22/07 <sup>±</sup> – 7/10/2013		3133 (71%)
Country of reporter	United States	4161
	Foreign	240
Report type	Expedited	4013
	Direct	104
	Periodic	284
Serious Outcomes*	Death	3315
	Life-threatening	102
	Hospitalized	854
	Other serious	870
Indication	None reported	3417
	Abuse	597
	Sleep aid	120
	Pain	80
	Hypersensitivity	37
	Cold/congestion	29
	Allergies	8
	Motion sickness	1
	Pre-medication	2
	Other	110
Case reported in literature	Yes	3047
	AAPCC-NPDS <sup>‡</sup>	2595
	No	1354

<sup>†</sup>These cases have not been deduplicated or assessed for an association with DPH.

\*A report may have one or more outcome

<sup>±</sup> Public Law 109-462, the Dietary Supplement and Nonprescription Drug Consumer Protection Act, signed December 22, 2006, provides for mandatory safety reporting for OTC human drug products not subject to applications approved under section 505 of the Act. The reporting requirements became effective December 22, 2007.

<sup>‡</sup>Published in the Annual Report of American Association of Poison Control Centers National Poison Data System

**8.8 APPENDIX H. DESCRIPTIVE CHARACTERISTICS OF FAERS CASES OF UNINTENTIONAL OVERDOSE REPORTED WITH DPH USE (N=268)**

<b>Table 10. Descriptive characteristics of Unintentional Overdose reported with DPH use, received by FDA from (January 1, 1969 – July 10, 2013) (N=268)†</b>		
Age (n=240)	Mean	31 years
	Median	34 years
	Range	2 months - 73 years
	≤17 years	25 % (n = 66)
Sex	Male	131
	Female	118
	Unknown	19
Report year	1969-1979	3
	1980-1989	5
	1990-1999	22
	2000-2009	178
	2010-2013	60
Reports from 12/22/07± – 7/10/2013		80 (30%)
Country of reporter	United States	258
	Foreign	10
Report type	Expedited	125
	Direct	12
	Periodic	131
Serious Outcomes*	Death	175
	Life-threatening	5
	Hospitalized	54
	Disability	1
	Other serious	66
Indication	None reported	188
	Accidental exposure	24
	Abuse	12
	Sleep aid	9
	Pain	25
	Hypersensitivity	5
	Cold/congestion	3
	Allergies	2
Case reported in literature	Yes	40
	AAPCC-NPDS‡	12
	No	228

†These cases have not been deduplicated or assessed for an association with DPH.

\*A report may have one or more outcome

± Public Law 109-462, the Dietary Supplement and Nonprescription Drug Consumer Protection Act signed December 22, 2006 provides for mandatory safety reporting for OTC human drug products not subject to applications approved under section 505 of the Act. The reporting requirements became effective December 22, 2007

‡Published in the Annual Report of American Association of Poison Control Centers National Poison Data System

**8.9 APPENDIX I. FAERS CASE NUMBERS, FAERS VERSION NUMBERS, AND MANUFACTURER CONTROL NUMBERS FOR ACCIDENTS CASE SERIES (N=37)**

FAERS Case #	FAERS Version #	Manufacturer Control #	FAERS Case #	FAERS Version #	Manufacturer Control #
3627175	1	001-0906-M0100053	6667338	1	US-JNJFOC-20080602538
3792441	1	200204-2026(0)	6908772	1	US-JNJFOC-20090202364
3970755	1	A0414626A	6915005	1	US-WYE-H06173408
3983279	1	2003105911	6996802	1	US-JNJFOC-20090502637
4155718	1	2004036150	7126985	1	US-JNJCH-2009025178
4172909	1	2004045151	7167155	1	US-JNJCH-2009028305
5822440	1	2005080533	7167912	1	US-JNJFOC-20091008552
5913807	2	2005138828	7269625	1	US-PERRIGO-10US006620
5927014	1	Not Applicable	7437053	1	US-JNJCH-2010014777
5991657	2	2006016304	7733685	1	US-B.I. PHARMACEUTICALS,INC./RI DGEFIELD-2010-BP-14743BP
6026810	1	2006039008	7775134	1	CHPA2011US01425
6123966	1	HQWYE227114J UN06	7799849	1	US-JNJCH-2011002528
6207588	1	Not Applicable	7953490	1	US-JNJFOC-20110504898
6456995	1	US-JNJFOC-20071008001	7994255	2	US-JNJFOC-20110605387
6467253	1	US-JNJFOC-20071102985	8361742	1	US-JNJFOC-20120111496
6471143	1	US-JNJFOC-20070902383	8383593	1	12AE001
6517634	1	S07-USA-06186-01	8685391	1	US-PFIZER INC-2012172757
6571881	1	US-PFIZER INC-2008017557	9097327	1	US-PERRIGO-13US001157
6649818	1	2008011661			

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/s/  
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CAROLYN A VOLPE  
10/29/2013

JOSEPH M TONNING  
10/29/2013

ALEX SECORA  
10/29/2013

TRACY M PHAM  
10/29/2013  
Drug use data were cleared for public release.

PETER S DIAK  
10/29/2013

ALLEN D BRINKER  
10/29/2013

CYNTHIA J KORNEGAY  
10/29/2013

HINA S MEHTA  
10/29/2013  
Drug use data cleared

JUDY A STAFFA  
10/29/2013

SCOTT E PROESTEL  
10/29/2013



**FOOD AND DRUG ADMINISTRATION**  
**CENTER FOR DRUG EVALUATION AND RESEARCH**  
DIVISION OF ANESTHESIA, ANALGESIA, AND ADDICTION PRODUCTS  
Bldg 22, Rm 3105 10903 New Hampshire Ave Silver Spring, MD  
Tel: (301) 796-2280

**Consult Response**

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**TO:** Division of Nonprescription Clinical Evaluation (DNCE)  
Jeffrey Buchanan, RPM

**FROM:** Ellen Fields, M.D., M.P.H.  
Clinical Team Leader, DAAAP

**THROUGH:** Sharon Hertz, M.D.  
Deputy Division Director, DAAAP

**THROUGH:** Bob Rappaport, M.D.  
Division Director, DAAAP

**SUBJECT:** NDA 205352 Aleve PM

**DATE:** October 18, 2013

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**Executive Summary**

- The Division of Nonprescription Clinical Evaluation (DNCE) requested that DAAAP review and evaluate NDA 205352 study reports 13053, 14837, 15881 with respect to the efficacy assessments for pain.
- NDA 205352 was submitted by Bayer Healthcare Consumer Care for a fixed-combination analgesic/sleep aid containing naproxen and diphenhydramine HCl, intended for over-the-counter use in patients ages 12 years and over.
- The Applicant conducted one pilot Phase 2 study (13053), and two key Phase 3 studies (14847 and 15881) to assess the efficacy of different doses naproxen/DPH in patients with dental pain due to third molar extractions and phase-advanced sleep.
- The primary endpoints in all studies were assessments of sleep and included Total Sleep Time (Phase 2 study only) ,Wake After Sleep Onset (WASO), and Sleep Latency (Phase 3 studies). Secondary assessments included sleep and analgesic endpoints. No adjustments were made in the statistical analysis plan for control of Type 1 error due to multiple endpoints.

- Secondary assessments for pain included categorical scales for pain intensity and pain relief, a patient global impression of the combination as a pain reliever, and rescue use (both amount and proportion of subjects requiring rescue).
- According to the Applicant, the studies demonstrated that the combination naproxen sodium 440mg/DPH 50mg was superior to its individual components for the primary endpoints.
- The secondary analgesia-related endpoints consistently demonstrated that naproxen behaved as an analgesic in combination with DPH, and a dose response was demonstrated between naproxen 440mg and naproxen 220mg. DPH alone did not appear to have analgesic properties.
- The analgesic-related variables and timing of assessments were acceptable.

### **Consult Request**

The Division of Nonprescription Clinical Evaluation (DNCE) requested that DAAAP review and evaluate studies 13053, 14837, 15881 with respect to the efficacy assessments for pain.

### **NDA Submission**

The Applicant, Bayer HealthCare Consumer Care (Bayer), submitted this New Drug Applicant (NDA) for a nighttime analgesic/sleep-aid, fixed-combination, over-the-counter (OTC) drug product containing naproxen sodium 220 mg and diphenhydramine hydrochloride (DPH) 25 mg per tablet. This product has been developed for the relief of occasional sleeplessness when associated with minor aches and pains, and the proposed use is for adults and children 12 years of age and over, to be taken as a 2-tablet dose before bedtime for no more than 10 consecutive days. Currently, there is no OTC nighttime analgesic/sleep-aid combination product available in the United States (US) that combines the naproxen sodium with DPH.

The Applicant conducted five clinical studies in support of this NDA. These studies included a pharmacokinetic study, a pilot efficacy study, two pivotal efficacy studies, and a multiple-dose safety study. According to the Applicant, based on the results from these studies, the naproxen sodium 440mg/DPH 50mg dose combination demonstrated statistically significant superiority and clinically meaningful treatment benefits in sleep parameters (wake after sleep onset [WASO] and sleep latency) compared with either naproxen sodium or DPH alone. The Applicant states that the combination was shown to be safe and well tolerated.

Naproxen sodium is a member of the arylpropionic acid group of nonsteroidal anti-inflammatory drugs (NSAIDs) with analgesic, anti-inflammatory, and antipyretic properties. Diphenhydramine hydrochloride is a first-generation antihistamine, an H1-receptor antagonist of the ethanolamine class used as a sedative, hypnotic, antihistamine, antitussive, and antiemetic agent in OTC products

Naproxen sodium has been marketed in the US in prescription form since 1976 under the tradename Naprosyn, and since 1994 as an OTC product under the tradename Aleve. It is currently approved as an OTC analgesic for the temporary relief of minor aches and

pains associated with the common cold, headache, toothache, muscular aches, and backache; for the minor pain of arthritis; for the pain of menstrual cramps; and for the reduction of fever. Naproxen sodium is approved in the US at OTC doses of 220 mg and 440 mg for use by adults and children at least 12 years of age or older. The Drug Facts Label instructs consumers not to take OTC naproxen sodium for more than 10 days for pain relief or more than 3 days for fever reduction unless otherwise directed by a physician.

Diphenhydramine hydrochloride, under the brand name Benadryl®, received marketing approval in the US in 1946 for use as a prescription antihistamine. Diphenhydramine hydrochloride and citrate salts have since been marketed as OTC sleep-aids since 1982 when they were included under the Monograph for Nighttime Sleep-Aid Drug Products for OTC Human Use, for use by adults and children 12 years of age or older at a dose of 50 mg at bedtime for the relief of occasional sleeplessness. Diphenhydramine hydrochloride and citrate salts have been used as one of the main ingredients in several marketed OTC analgesic/nighttime sleep aid combination products, such as Tylenol® PM, Bayer® PM, Excedrin® PM, Motrin® PM, and Advil® PM.

### **Regulatory History Relevant to Analgesia**

At the PIND meeting held on February 10, 2009, DNCE agreed that the following proposed secondary pain endpoints were acceptable; change from baseline pain intensity on categorical and VAS scales, pain relief score on a categorical scale, time to rescue medication and cumulative proportion of subjects taking rescue by hour, and global assessment as a pain reliever. DAAAP was not consulted to take part in this meeting.

DAAAP was asked to review the analgesia-related aspects of the protocol for Study 14837 submitted as a Special Protocol Assessment on November 25, 2009. It was a Phase 3, multi-center, double-blind, randomized, parallel-group, single-dose study assessing the analgesic and hypnotic effect of naproxen sodium and DPH combination in subjects with post-operative dental pain and phase-advanced sleep. Pain assessments were limited to overall pain intensity difference, pain relief, time to analgesic rescue, and proportion of subjects taking rescue in this setting because of the potential interference of sleep by the evaluation of periodic pain measurements before and during sleep. DAAAP was in agreement with the proposed assessments of analgesia, however a SPA was not granted due to concerns raised by DNCE and DNP regarding dose selection, sleep assessments, and statistical analyses.

DAAAP also reviewed the protocol for Study 15881, submitted on November 18, 2011, which was a Phase 3, multicenter, randomized, double-blind, parallel-group trial assessing efficacy and safety of naproxen/DPH in post-surgical dental pain with advanced phase sleep. The proposed pain assessments listed as secondary efficacy endpoints were the same as in Study 14837 and were acceptable to DAAAP.

### **Summary of Clinical Development Program**

The Applicant initiated the clinical program with a pilot study (Study 13053) to evaluate whether naproxen sodium taken in combination with DPH would provide added clinical

benefit over naproxen sodium when taken alone in subjects with postoperative pain and phase-advanced sleep. The primary endpoint of this study was total sleep time measured by actigraphy. Wake after sleep onset (WASO) and sleep latency by actigraphy, as well as other subjective sleep and pain assessments, were secondary endpoints. This study did not utilize the to-be-marketed formulation of the combination product, but used the individual approved components (naproxen sodium 220mg and DPH 25mg) which were demonstrated in the PK study to be bioequivalent to the to-be-marketed combination formulation. According to the Applicant this study provided a strong rationale for developing the combination product.

Following the pilot study, the Applicant conducted two Phase 3 efficacy studies, 14837 and 15881, to evaluate various doses of the combination product. Study 14837 was conducted to evaluate the efficacy of two different dose combinations of naproxen sodium and DPH (naproxen sodium 440mg/DPH50mg and naproxen sodium 220mg/DPH 50mg). The objective of this study was to assess if a single oral dose of the naproxen sodium/DPH combination taken prior to bedtime provided added clinical benefit for improving sleep (WASO and sleep latency) than either single ingredient taken alone. In addition, the study was designed to assess a dose-response relationship between the high dose and low dose of naproxen sodium in the combination products. Based on the results from this study, the Applicant conducted a second efficacy study (Study 15881) to evaluate the efficacy of the combination with a lower dose of DPH, naproxen sodium 440mg/DPH 25 mg, in subjects with postoperative pain and phase-advanced sleep.

All three efficacy studies utilized the dental pain model. Traditional pain assessments such as repeated assessments of pain intensity and pain relief over the treatment period were not used in the efficacy studies because the target population was subjects with sleeplessness associated with pain, and the primary purpose of the studies was to assess the impact of the treatment on sleep. It would have been inappropriate to wake subjects to assess their pain levels. Instead, the subjects' pain levels were assessed after waking using validated categorical scales.

### **Individual Studies**

The following summaries focus on the analgesic assessments and results of the secondary endpoints related to pain. Additional details regarding these studies may be found in the DNCE and DNP NDA reviews.

#### **Pilot Efficacy Study 13053**

This was a single-center, double-blind, randomized, single-dose study assessing the analgesic and hypnotic effect of naproxen sodium and DPH combination, in subjects with post-operative dental pain and phase-advanced sleep. The objective of the study was to evaluate the analgesic and hypnotic efficacy of naproxen sodium and diphenhydramine combination when compared to naproxen sodium, diphenhydramine, and an ibuprofen and diphenhydramine combination.

A total of 191 otherwise healthy subjects 16-45 years of age, were screened. Subjects underwent surgical removal of one to three impacted third molars (one of which had to be at least a partial bony mandibular impaction), had moderate to severe postoperative pain on the Categorical Pain Rating Scale, and had a score of  $\geq 50$  mm on the 100-mm pain visual analog scale (VAS) prior to randomization. Concomitant medications were appropriately excluded. Surgery was scheduled in the late afternoon, and postoperatively subjects were asked to rate their pain intensity on a 4-point Categorical Pain Rating Scale and score the pain VAS. Subjects who had moderate to severe postoperative pain on the Categorical Pain Rating Scale and a score of  $\geq 50$  mm on the VAS scales were randomly assigned to one of six treatment groups, received the assigned investigational product, and then were instructed to go to sleep.

Of the 191 subjects screened, 162 were randomized to one of the six treatment groups (27 subjects in each treatment group).

- Naproxen sodium 440mg/DPH 50mg combination taken as 2 Aleve (naproxen sodium 220 mg tablets) + 2 Benadryl (DPH 25 mg tablets)
- Naproxen sodium 440 mg taken as 2 Aleve + 2 placebo tablets
- Naproxen sodium 220mg/DPH 50mg combination taken as 1 Aleve + 2 Benadryl + 1 placebo tablet
- Naproxen sodium 220mg taken as 1 Aleve + 3 placebo tablets
- DPH 50 mg taken as 2 Benadryl + 2 placebo tablets
- Advil PM taken as 2 Advil PM (ibuprofen 200 mg and diphenhydramine citrate 38 mg caplets) + 2 placebo tablets

Subjects who did not wake on their own were awakened no sooner than 10 hours post dose. Rescue analgesic medication was administered at any time at the request of the patient if pain intensity was not reduced and adequate pain relief was not achieved, or on return of pain. Rescue medication was Lortab 5mg tablets. In cases of extreme pain, IV tramadol was available. Subjects were required to complete pain assessments immediately prior to taking rescue for the first time.

The primary efficacy parameter was total sleep time measured by actigraphy, and was measured from the time of lights out until actigraphy indicated waking or subject requested rescue medication.

There were a number of secondary efficacy assessments regarding sleep and pain. Those related to pain included:

- **Categorical Pain Severity Rating**
  - Upon awakening, the patient was asked to finish the statement: “my pain at this time is” by checking the appropriate box.
    - No Pain (0)
    - Mild Pain (1)
    - Moderate Pain (2)
    - Severe Pain (3)

- **Visual analog (100-mm) pain severity rating scale**

Mark the line below to indicate the severity of the pain you are experiencing.

No Pain |-----| Possible Pain  
Worse

- **Categorical pain relief rating scale**

Upon awakening, the patient was asked to finish the statement: “overall, the relief from my starting pain was” by checking the appropriate box.

- No Relief (0)
- A Little Relief (1)
- Some Relief (2)
- A Lot of Relief (3)
- Complete Relief (4)

- **Global assessment of pain**

Upon awakening, the patient was asked “how would you rate the study medication as a pain reliever?”

- Poor (0)
- Fair (1)
- Good (2)
- Very Good (3)
- Excellent (4)

- Time to rescue medication, the cumulative proportion of subjects taking rescue medication by hour, and the number of times subjects took rescue medication were also measured as secondary pain assessments.

The primary treatment groups for comparison were:

- Naproxen sodium 440mg/DPH 50mg combination versus naproxen sodium 440mg
- Naproxen sodium 440 mg/DPH 50mg combination versus DPH 50mg
- Naproxen sodium 220mg/DPH 50mg combination versus naproxen sodium 220mg
- Naproxen sodium 220mg/DPH50mg combination versus DPH 50mg
- Naproxen sodium 440mg/DPH 50mg combination versus ibuprofen 400mg/diphenhydramine citrate 76mg combination
- Naproxen sodium 220 mg/DPH 50mg combination versus ibuprofen 400mg/diphenhydramine citrate 76mg combination

All efficacy analyses were based on the intent-to-treat population that included all randomized subjects who received treatment, and provided at least one efficacy assessment. In this study, all randomized subjects met these criteria.

There was no adjustment for multiple comparisons.

Results

All randomized subjects completed the study.

The mean age of subjects in the study was 19 years with a range of 16 to 30 years. Fifty-two percent of the subjects were female, and 97% were white. Approximately 59% of subjects had moderate pain at baseline and 41% had severe pain. The treatment groups were similar in their demographics except that the DPH group had 70% females, and the Advil PM group had fewer subjects with severe baseline pain (22%).

The Applicant's results of the primary endpoint, total sleep time as measured by actigraphy, showed that the addition of DPH to naproxen provided benefit over naproxen alone in the study population. Numerically, total sleep time was greater for naproxen 220mg/DPH 50mg than naproxen 440mg/DPH 50mg. The only statistically significant differences were between naproxen 440mg/DPH 50mg and DPH 50mg alone, and naproxen 220mg/DPH 50mg and DPH 50mg alone. The combinations were numerically superior to naproxen alone and ibuprofen alone, but did not demonstrate statistical significance. Secondary sleep endpoints generally supported an advantage of the combination of naproxen and DPH over the individual components.

Objective Sleep Parameters	Aleve 440 mg / DPH (n=27)	Aleve 440 mg (n=27)	Aleve 220 mg / DPH (n=27)	Aleve 220 mg (n=27)	DPH (n=27)	Advil PM (n=27)
Total sleep time (Minutes)	340*	305	414*	309	76	336
Sleep efficiency (%)	57*	51	69*	52	13	57
WASO (Minutes)	140*	191	76*	146	428	129
Sleep Latency (Minutes)	29	33	47	32	41	36
* p < 0.05 vs DPH DPH = diphenhydramine HCL 50 mg						

Source: Study report p. 8

The following tables and figures from the Applicant's study report summarize the numerical results of the pain assessment analyses. The Applicant's statistical analyses and p-values are not included because these analyses were not adjusted for multiple endpoints.

Similar improvement in the categorical pain scale was noted for both naproxen/DPH combinations, and the least improvement was for DPH alone. Change from baseline in pain intensity VAS, overall pain relief, and global impression of drug as a pain reliever

followed the same trend, although for pain intensity VAS naproxen 220mg/DPH performed slightly better numerically than naproxen 440mg/DPH.

Time to analgesic rescue is shown in the Kaplan Meier curve below (Figure X). The DPH treatment group required rescue much sooner than all other treatment groups. The difference in time to rescue for all other groups was fairly similar. Over 90% of patients in the DPH group required rescue analgesia, over 40% in naproxen 440mg/DPH and naproxen 440mg groups, and approximately 30% in the naproxen 220mg/DPH. All subjects who received rescue medication took it once, with the exception that 11% of patients in the DPH group took rescue medication twice.

**Table 11-18: Analysis Results for Categorical Pain Rating Scale Score (Change from Baseline)**

	Aleve 440mg /DPH	Aleve 440mg	Aleve 220mg /DPH	Aleve 220mg	DPH	Advil PM
<b>N</b>	27	27	27	27	27	27
LSM (SE)	-1.2 (0.18)	-1.0 (0.18)	-1.2 (0.18)	-0.7 (0.18)	0.3 (0.18)	-0.9 (0.18)
95% CI	-1.5 - -0.8	-1.3 - -0.6	-1.5 - -0.8	-1.0 - -0.3	-0.1 - 0.6	-1.3 - -0.6

Source: Clinical Study Report, p. 72

**Table 11-19: Analysis Results for VAS Score (Change from Baseline)**

VAS Score (Change from Baseline)	Aleve 440mg /DPH	Aleve 440mg	Aleve 220mg /DPH	Aleve 220mg	DPH	Advil PM
<b>N</b>	27	27	27	27	27	27
LSM (SE)	-44.0 (5.61)	-36.7 (5.61)	-47.3 (5.62)	-25.9 (5.63)	6.0 (5.63)	-35.9 (5.64)
95% CI	-55.1 - -33.0	-47.7 - -25.6	-58.4 - -36.2	-37.0 - -14.8	-5.1 - 17.1	-47.0 - -4.8

Source: Clinical Study Report, p. 74

**Table 11-20: Analysis Results for Overall Pain Relief Rating Scale Score**

	Aleve 440mg /DPH	Aleve 440mg	Aleve 220mg /DPH	Aleve 220mg	DPH	Advil PM
<b>N</b>	27	27	27	27	27	27
Some relief	8 (29.6%)	7 (25.9%)	5 (18.5%)	4 (14.8%)	5 (18.5%)	5 (18.5%)
A lot relief	12 (44.4%)	10 (37.0%)	13 (48.1%)	11 (40.7%)	2 (7.4%)	13 (48.1%)
Complete relief	2 (7.4%)	3 (11.1%)	4 (14.8%)	3 (11.1%)	0 (0.0%)	3 (11.1%)
Total	22 (81.4%)	20 (74.0%)	22 (81.4%)	18 (66.6%)	7 (25.9%)	21 (77.7%)

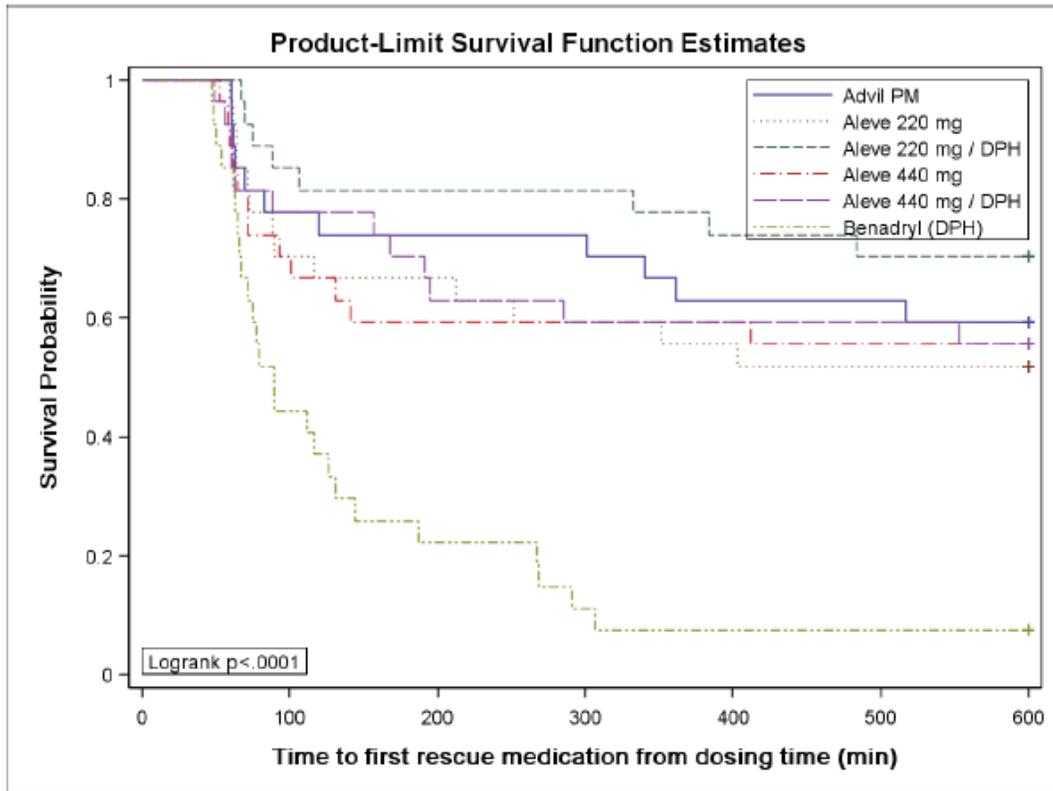
Source: Clinical Study Report, p. 76

**Table 11-21: Analysis Results for Global Assessment of Study Medication as a Pain-Reliever**

	Aleve 440mg /DPH	Aleve 440mg	Aleve 220mg /DPH	Aleve 220mg	DPH	Advil PM
<b>N</b>	27	27	27	27	27	27
Good	7 (25.9%)	7 (25.9%)	4 (14.8%)	7 (25.9%)	5 (18.5%)	4 (14.8%)
Very good	11 (40.7%)	4 (14.8%)	9 (33.3%)	9 (33.3%)	0 (0.0%)	11 (40.7%)
Excellent	2 (7.4%)	5 (18.5%)	7 (25.9%)	1 (3.7%)	0 (0.0%)	2 (7.4%)
Total	20 (74.0%)	16 (59.2%)	20 (74.0%)	17 (62.9%)	5 (18.5%)	17 (62.9%)

Source: Clinical Study Report, P. 78

**Figure 11-2 Kaplan-Meier survival curve of time to rescue medication**



Source: Clinical Study Report, p. 79

Table 14.2.19  
Frequency of Number of Times Subjects Took Rescue Medications, Intent-to-Treat Population

Number of Times Subjects Took Rescue Medications	Aleve 440 mg/DPH [1] (N=27)	Aleve 440 mg (N=27)	Aleve 220 mg/DPH [1] (N=27)	Aleve 220 mg (N=27)	DPH [1] (N=27)	Advil PM (N=27)
0	15 (55.6%)	15 (55.6%)	19 (70.4%)	14 (51.9%)	2 (7.4%)	16 (59.3%)
1	12 (44.4%)	12 (44.4%)	8 (29.6%)	13 (48.1%)	22 (81.5%)	11 (40.7%)
2	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (11.1%)	0 (0.0%)
3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Overall (any rescue medication)	12 (44.4%)	12 (44.4%)	8 (29.6%)	13 (48.1%)	25 (92.6%)	11 (40.7%)

[1] DPH = Diphenhydramine 50 mg.

Source: Clinical Study Report, p. 143

### Discussion

This was a Phase 2, double-blind, factorial design study that assessed the efficacy of two naproxen/DPH combinations compared to the individual components and an ibuprofen/diphenhydramine citrate combination product. While the study did not include the to-be-marketed formulation of Aleve PM, the individual naproxen and diphenhydramine products used were shown to be bioequivalent to the TBM formulation in Study 16135, therefore the study results are applicable to the final product.

The study was designed appropriately from the perspective of assessment of analgesia. The study population, patients undergoing third molar extraction, is commonly used in studies of analgesics intended for acute pain treatment. Because the study drug is intended for the relief of occasional sleeplessness associated with minor aches and pains and to help patients fall asleep, the primary endpoint was sleep related. The Applicant appropriately included secondary endpoints to assess the analgesic efficacy of the combination product.

The analgesic assessment measures included in the protocol, a categorical pain relief scale, a categorical pain severity scale, a VAS pain severity scale, and a global impression scale were appropriate. In the setting of a drug product intended to aid sleep, it is not possible to assess pain at frequent intervals post-dosing, and therefore it is necessary to obtain pain assessments upon the study subject awakening. While the assessments after waking have some limitations in that they require recall, the Applicant did capture use of and time to analgesic rescue medication, which also informs analgesic efficacy.

The primary endpoint demonstrated statistically significant superiority in terms of efficacy for both the naproxen/DPH combinations compared to DPH alone, but not compared to naproxen alone. Of note, the naproxen 220mg/DPH 50mg was numerically superior to naproxen 440mg/DPH 50mg for total sleep time. The secondary pain endpoints demonstrated numerical superiority of both combinations over DPH alone and naproxen alone, although in some instances the differences were small.

From the pain assessment perspective, this study was appropriately designed with inclusion of acceptable analgesic endpoints, and the results demonstrated some advantage of both doses of the combination product (naproxen 220mg + DPH and

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naproxen 440mg + DPH) over the individual components in terms of analgesia. As a Phase 2 study these results appear adequate to inform the subsequent Phase 3 trials.

### **Phase 3 Study 14837**

This was a multi-center, double-blind, randomized, parallel-group, single-dose study assessing the analgesic and hypnotic effect of naproxen sodium and DPH combination in subjects with post-operative dental pain and phase-advanced sleep. The objective of the study was to demonstrate that the analgesic and hypnotic efficacy of a single oral dose of two dose combinations of a naproxen sodium and diphenhydramine combination provides added clinical benefit to sleep improvement than either single ingredient alone.

The study included a Screening Visit, a Dosing Period, and an End of Trial assessment. Subjects who had undergone surgical extraction of impacted third molars were housed and observed at a clinical research unit overnight and were required to go to bed approximately 5 hours earlier than usual. After surgery (scheduled between 1330 h and 1530 h), subjects who experienced postsurgical pain of at least moderate severity (between 1600 h and 1830 h) were randomized to one of the four treatment groups. The effects of a single-dose administration of investigational product on sleep during the Dosing Period were evaluated objectively using actigraphy. Subjective sleep questionnaires, categorical pain scales, and global assessments were also used to evaluate the efficacy of the investigational products.

Rescue medication (Lortab, hydrocodone 5mg/APAP 500mg) was allowed if pain intensity was not reduced and adequate pain relief was not achieved any time after administration of study drug, although subjects were encouraged to wait 60 minutes. In cases of extreme pain, the investigator could administer appropriate analgesics. Pain assessments were completed immediately prior to first rescue use.

The study population consisted of healthy male and females ages 12 years and above with impacted third molars, who were scheduled to undergo surgical removal of a minimum of two third molars, at least one of which had to be a mandibular third molar. Subjects had moderate to severe postoperative pain on a categorical pain rating scale, and a score of at least 50mm on a 100-mm pain severity VAS. Subjects with serious sleep disorders that did not respond to OTC treatment and required a prescription hypnotic or sedative were excluded.

A total of 712 subjects were randomized, all of whom were included in the efficacy and safety assessments. Subjects were randomized to the following treatment groups. This study utilized the to-be-marketed formulations of the naproxen/DPH combinations:

- Naproxen sodium 440mg/DPH 50mg administered as 2 X naproxen sodium 220mg/DPH 25mg tablets (n=203)
- Naproxen sodium 220mg/DPH 50mg administered as 1 naproxen sodium 220mg/DPH 50mg tablet (n=204)
- Naproxen sodium 440mg administered as 2 X naproxen sodium 220mg (n=203)
- DPH 50mg administered as 2 X DPH 25 mg (n=102)

Subjects were awakened after 10 hours of sleep if they did not awaken spontaneously.

The primary efficacy parameters, sleep and wakefulness, were measured by actigraphy, and were used to determine time spent awake after sleep onset (WASO) and sleep latency, as well as total sleep time and sleep efficiency. The primary efficacy variables were WASO (naproxen/DPH vs. naproxen) and sleep latency (naproxen/DPH vs. DPH).

Secondary objective sleep variables obtained by actigraphy were total sleep time and sleep efficiency. Subjective secondary sleep variables included a Global Assessment of Investigational Product as a Sleep-Aid, Subjective Sleep Questionnaire, and Karolinska Sleep Diary.

Secondary pain variables were similar to those in the Phase 2 study (see complete description of endpoints in Phase 2 study section) and included change from baseline in categorical pain rating scale, categorical pain relief scale, time to analgesic rescue medication, cumulative proportion of subject taking rescue medication by hour, and Global Assessment of Investigational Product as a Pain Reliever.

The ITT population (randomized, received study drug, and had at least one efficacy assessment) was used for efficacy analyses. The primary endpoint, WASO and sleep latency, was analyzed using a hierarchical testing procedure in order to protect the overall Type 1 error at the 0.05 level. There was no adjustment for multiple endpoints for secondary endpoint analyses.

### Results

The ITT population was comprised of all 712 randomized subjects, as they all received treatment and had at least one efficacy assessment. Only three subjects did not complete the study, all in the DPH 50mg group.

Demographic characteristics were generally comparable among treatment groups. The mean age was 21 years, ranging from 16 to 48 years, 57% of the subjects were female, and 89% were white. Overall, 69% of subjects rated their baseline pain as moderate, and 31% severe. The mean VAS pain score at baseline was 72/100mm.

### *Primary endpoints*

The primary endpoint analyses were each conducted using a hierarchical testing procedure (separately for WASO and sleep latency) in order to protect the overall Type I error at the 0.05 level. The Applicant's analyses for WASO showed that the naproxen sodium 440mg/DPH 50mg group had the shortest WASO time (LS mean 143.7 minutes) compared with the naproxen sodium 220mg/DPH 50mg group (LS mean 230.9 minutes) and the naproxen sodium 440mg group (LS mean 214.0 minutes). The DPH 50mg group had the longest WASO time (LS mean 431.4 minutes).

The difference between the naproxen sodium 44 mg/DPH 50mg and the naproxen sodium 440 mg groups was statistically significant ( $P = 0.0002$ ); however, the difference between the naproxen sodium 220mg/DPH 50mg group and the naproxen sodium 440mg group

was not ( $P = 0.3627$ ). In addition, the difference between the naproxen sodium 440mg/DPH 50mg group and the naproxen sodium 220mg/DPH 50mg group was statistically significant ( $P < 0.0001$ ), demonstrating that naproxen sodium 440mg/DPH 50mg had significantly shorter WASO time than naproxen sodium 220mg/DPH 50mg.

For Sleep Latency as measured by actigraphy, the naproxen sodium 440mg/DPH 50mg and naproxen sodium 440mg groups had similar times to sleep onset (median of 25.50 minutes and 25.75 minutes, respectively). In the naproxen sodium 220mg/DPH 50mg group, subjects had a longer time to sleep onset (median of 30.25 minutes). The DPH 50mg group had the longest time to sleep onset (median of 41.5 minutes).

Differences between both the naproxen sodium 440mg/DPH 50 mg and naproxen sodium 220mg/DPH 50mg groups compared with the DPH 50mg group were statistically significant ( $P < 0.0001$  and  $P = 0.0003$ , respectively). The difference between the naproxen sodium 440mg/DPH 50mg group and the naproxen sodium 220mg/DPH 50mg group also was statistically significant ( $P = 0.0096$ ), demonstrating that naproxen sodium 440mg/DPH 50mg had significantly shorter time to sleep onset than naproxen 220mg/DPH 50mg.

The secondary endpoints related to sleep generally supported findings for the primary endpoints.

#### *Secondary pain endpoints*

Secondary endpoint analyses for pain severity assessments were analyzed using an ANCOVA model. If a subject took rescue medication, the worst score before rescue medication administration was carried forward to the morning score. Time to rescue medication was estimated using the Kaplan Meier method and logrank test for pairwise comparisons. There was no correction of the secondary endpoint analyses for multiple endpoints, therefore the Applicant's p-values are merely descriptive in this setting.

#### *Pain intensity*

Pain intensity was collected on a 4-point categorical scale, where 0= no pain and 3= severe pain. This was measured upon morning awakening, or when the subject requested rescue analgesia, whichever came first. The subject was asked to complete the following sentence, "my pain at this time is....." by selecting the appropriate number. The naproxen sodium 440mg/DPH 50mg, naproxen sodium 220mg/DPH 50mg, and naproxen sodium 440mg all reported a mean reduction in pain intensity from baseline of approximately 1.0 point. The DPH 50mg group had no reduction in pain intensity from baseline. The naproxen 440mg/DPH 50mg group had a slightly greater reduction in pain than the naproxen 220mg/DPH 50mg combination. The Applicant's summary of pain intensity changes from baseline by treatment group is shown below.

**Table 18 Summary of pain intensity and change from baseline (Intent-to-Treat Population)**

Visit	Statistic	Treatment Group			
		NP 440 mg/ DPH 50 mg N = 203	NP 220 mg/ DPH 50 mg N = 204	NP 440 mg N = 203	DPH 50 mg N = 102
Day 1 (Baseline)	Mean	2.3	2.3	2.3	2.3
	Standard deviation	0.45	0.48	0.46	0.45
	Median	2.0	2.0	2.0	2.0
	Minimum	2	2	2	2
	Maximum	3	3	3	3
Post-baseline	Mean	1.1	1.6	1.4	2.4
	Standard deviation	0.96	1.05	1.02	0.85
	Median	1.0	1.0	1.0	3.0
	Minimum	0	0	0	0
	Maximum	3	3	3	3
Change from Baseline	Mean	-1.2	-0.7	-0.9	0.1
	Standard deviation	1.01	1.05	0.99	0.82
	Median	-1.0	-1.0	-1.0	0.0
	Minimum	-3	-3	-3	-2
	Maximum	1	1	1	1

0 = No Pain, 1 = Mild Pain, 2 = Moderate Pain, and 3 = Severe Pain.

Negative changes from baseline imply a reduction in pain intensity from baseline.

If rescue medication was taken, the worst score prior to rescue including baseline was carried forward to the morning score and used for analysis.

DPH = diphenhydramine hydrochloride; NP = naproxen sodium.

Source: Study Report, p. 78

### *Pain Relief*

Pain relief was collected on a 5-point categorical scale, where 0= no relief and 4= complete relief. This was measured upon morning awakening. If rescue medication was used during the night, a score of “0” was used for the morning rating of pain relief. The subject was asked to complete the following sentence, “overall, the relief from my starting pain is.....” by selecting the appropriate number.

The overall median response for both the naproxen sodium 440mg/DPH 50mg group and the naproxen sodium 440mg group was 3.0, corresponding to a rating of “a lot of relief.” The naproxen sodium 220mg/DPH 50mg group had a median response of 2.0, corresponding to a rating of “some relief.” The DPH 50mg group had a median response of zero, corresponding to a rating of “no relief.” These results were also supported by mean values that showed the same trend as the median values, with mean responses of 2.4, 2.0, 1.7, and 0.6 for the naproxen sodium 440mg/DPH 50mg group, the naproxen sodium 440mg group, the naproxen sodium 220mg/DPH 50mg group, and the DPH 50mg group, respectively. The naproxen sodium 440mg/DPH 50mg group had greater pain relief compared with the naproxen sodium 220mg/DPH 50mg group, the naproxen sodium 440mg group, and the DPH 50mg group. The naproxen sodium 440mg group also had greater pain relief than the naproxen sodium 220mg/DPH 50 mg group. The Applicant’s table below shows these results.

**Table 21 Summary of pain relief scale results (Intent-to-Treat Population)**

Pain relief scale parameter	Treatment Group			
	NP 440 mg/ DPH 50 mg N = 203	NP 220 mg/ DPH 50 mg N = 204	NP 440 mg N = 203	DPH 50 mg N = 102
Number of subjects in analysis	203	204	202	102
0 = no relief	44 (21.7)	89 (43.6)	68 (33.5)	79 (77.5)
1 = a little relief	4 (2.0)	4 (2.0)	8 (3.9)	1 (1.0)
2 = some relief	32 (15.8)	29 (14.2)	24 (11.8)	11 (10.8)
3 = a lot of relief	65 (32.0)	53 (26.0)	62 (30.5)	8 (7.8)
4 = complete relief	58 (28.6)	29 (14.2)	40 (19.7)	3 (2.9)
Mean	2.4	1.7	2.0	0.6
Median	3.0	2.0	3.0	0.0
Standard deviation	1.47	1.58	1.58	1.14
Minimum	0	0	0	0
Maximum	4	4	4	4

If rescue medication was taken, the score of 0 (no relief) was used for the morning's rating of pain relief.

DPH = diphenhydramine hydrochloride; NP = naproxen sodium.

Source: Study Report p. 80

*Global Assessment of Investigational Product as a Pain Reliever*

This assessment was collected on a 5-point categorical scale, where 0= poor and 4= excellent, and was measured upon morning awakening. The subject was asked to answer the following question, “overall, how would you rate the medication as a pain reliever?” by selecting the appropriate number.

The mean responses were similar for the three treatment groups that included naproxen, and lower for the DPH only group. The median values also trended similarly. All naproxen groups had a median value of 3, which corresponds to a rating of “very good” on the global assessment scale.

**Table 23 Analysis of Global Assessment of Investigational Product as a Pain Reliever: summary (Intent-to-Treat Population)**

Response statistic	Treatment Group			
	NP 440 mg/ DPH 50 mg N = 203	NP 220 mg/ DPH 50 mg N = 204	NP 440 mg N = 203	DPH 50 mg N = 102
Number of subjects included in the analysis	166	126	141	25
0 = Poor	2 (1.0)	2 (1.0)	0	4 (3.9)
1 = Fair	9 (4.4)	16 (7.8)	15 (7.4)	5 (4.9)
2 = Good	43 (21.2)	35 (17.2)	36 (17.7)	9 (8.8)
3 = Very good	64 (31.5)	48 (23.5)	56 (27.6)	7 (6.9)
4 = Excellent	48 (23.6)	25 (12.3)	34 (16.7)	0
Mean	2.9	2.6	2.8	1.8
Standard deviation	0.93	0.99	0.94	1.05
Median	3.0	3.0	3.0	2.0
Minimum	0	0	1	0
Maximum	4	4	4	3

DPH = diphenhydramine hydrochloride; NP = naproxen sodium.

Source: Study Report, p. 81

*Rescue medication use*

The cumulative proportion of subjects taking rescue medication was calculated as the number of subjects who had taken rescue medication at a given time divided by the number subjects treated.

During the first 60 minutes after dosing, only one subject requested rescue (naproxen 220mg/DPH 50mg group). At all post-dose time points after the first 60 minutes, the naproxen sodium 440mg/DPH 50mg had the lowest proportion of subjects taking rescue medication, followed by the naproxen sodium 440mg group and the naproxen sodium 220mg/DPH 50 mg group. At all post-dose time points after the first 60 minutes, the DPH 50 mg group had the highest proportion of subjects taking rescue medication.

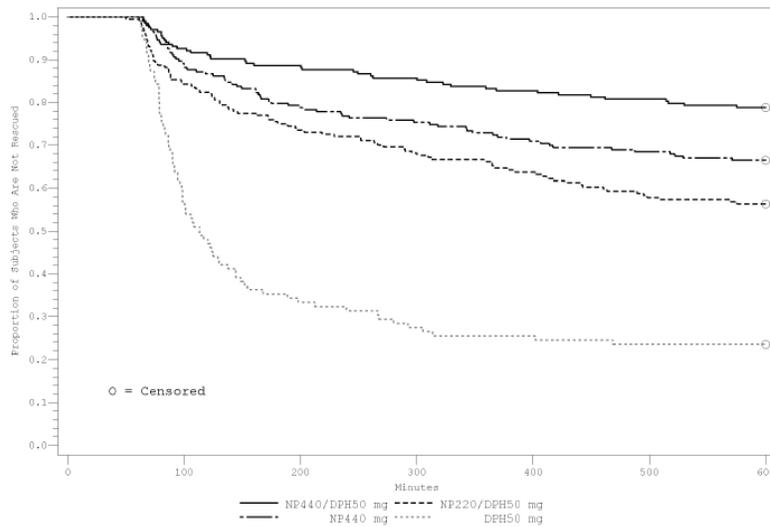
**Table 13 Cumulative proportion of subjects taking rescue medication (Safety Population)**

Time After Dosing That Rescue Medication Was Taken	Treatment Group							
	NP 440 mg/ DPH 50 mg N = 203		NP 220 mg/ DPH 50 mg N = 204		NP 440 mg N = 203		DPH 50 mg N = 102	
	n	(%)	n	(%)	n	(%)	n	(%)
≤ 60 minutes	0		1	(0.5)	0		0	
≤ 120 minutes	18	(8.9)	36	(17.6)	27	(13.3)	53	(52.0)
≤ 180 minutes	23	(11.3)	50	(24.5)	41	(20.2)	66	(64.7)
≤ 240 minutes	25	(12.3)	57	(27.9)	47	(23.2)	70	(68.6)
≤ 300 minutes	29	(14.3)	65	(31.9)	50	(24.6)	74	(72.5)
≤ 360 minutes	34	(16.7)	69	(33.8)	55	(27.1)	76	(74.5)
≤ 420 minutes	36	(17.7)	78	(38.2)	62	(30.5)	77	(75.5)
≤ 480 minutes	39	(19.2)	83	(40.7)	63	(31.0)	78	(76.5)
≤ 540 minutes	42	(20.7)	87	(42.6)	67	(33.0)	78	(76.5)
≤ 600 minutes	43	(21.2)	89	(43.6)	68	(33.5)	78	(76.5)

Source: Study report p. 66

Time to rescue medication use was assessed using a Kaplan-Meier analysis. Subjects who did not take rescue medication were censored at 10 hours for time to rescue. The following figure illustrates that the DPH only group took rescue much earlier than the naproxen groups.

**Figure 4** Box plot for time to rescue medication taken (Intent-to-Treat Population)



Source: Study report, p. 83

The number of times subjects took rescue is summarized below.

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Table 14.2.13  
Number of Times Subjects Took Rescue Medication (ITT Population)

Number of Times Subjects Took Rescue Medication	Treatment Group			
	NP 440 mg/DPH 50 mg N=203	NP 220 mg/DPH 50 mg N=204	NP 440 mg N=203	DPH 50 mg N=102
0	160 ( 78.8)	115 ( 56.4)	135 ( 66.5)	24 ( 23.5)
1	39 ( 19.2)	79 ( 38.7)	60 ( 29.6)	48 ( 47.1)
2	4 ( 2.0)	10 ( 4.9)	8 ( 3.9)	28 ( 27.5)
3	0	0	0	2 ( 2.0)

N = Number of subjects in the ITT Population.  
NP: Naproxen Sodium DPH: Diphenhydramine Hydrochloride.

Source: Study report, p. 168

The majority of subjects in the three naproxen groups did not take any rescue, while the majority of subjects in the DPH only group did. Of the three naproxen groups the naproxen 220mg/DPH 50mg had the largest proportion of subjects taking rescue medication, and the largest taking proportion taking more than one dose.

### Discussion

According to the Applicant's analyses, the primary efficacy results demonstrated that naproxen sodium 440mg/DPH 50mg was the only treatment group shown to be significantly more effective than either single ingredient alone for both WASO and sleep latency. Naproxen 220mg/DPH 50mg failed to show superiority over naproxen sodium 440mg for WASO but did show superiority for sleep latency. Of note, there was not a treatment group for naproxen 220mg alone, which would have been a more reasonable comparator for the naproxen 220mg/DPH 50mg group, as it is likely naproxen 440mg would provide better analgesic efficacy than 220 mg. The secondary efficacy results for sleep assessments were overall consistent with the primary efficacy results.

For analgesic efficacy, the assessments employed in this study, categorical pain intensity and pain relief scales, and the global impression of the study treatment as a pain reliever are acceptable. The Applicant did not include a more granular scale to assess pain intensity, such as a visual analog scale or numerical rating scale, which is preferable when assessing pain intensity changes in analgesic studies, particularly as a primary endpoint. However because the pain assessments in this study were secondary and intended to confirm the analgesic efficacy of naproxen, the categorical scales are adequate.

The results demonstrated that naproxen 440mg alone and in combination with DPH 50mg were more effective than naproxen 220mg/DPH 50mg in terms of analgesia. These results were consistent for all of the pain assessments, the global assessment, and rescue medication use. It is expected that there would be a dose response for analgesic efficacy for the 220mg naproxen and the 440mg naproxen.

### **Phase 3 Study 15881**

This was a multi-center, double-blind, randomized, parallel-group, single-dose study assessing the efficacy and safety of naproxen sodium and DPH combination in subjects with post-operative dental pain and phase-advanced sleep. The objective of the study was to demonstrate that the analgesic and hypnotic efficacy of a single oral dose naproxen 440mg in combination with DPH 25mg was superior to naproxen 440mg and DPH 50mg alone.

The study included a Screening Visit, a Dosing Period, and an End of Trial (EOT) assessment. Subjects who had undergone surgical extraction of impacted third molars were housed and observed at a clinical research unit overnight and were required to go to bed approximately 5 hours earlier than usual. After surgery, subjects who experienced postsurgical pain of at least moderate severity (moderate-to-severe postoperative pain on the Categorical Pain Rating Scale and a score of  $\geq 50$  mm on the Pain Severity VAS) were randomized to one of the three treatment groups. The effects of a single-dose administration of investigational product on sleep were evaluated objectively using actigraphy. Subjective sleep questionnaires, categorical pain scales, and global assessments were also used to evaluate the efficacy of the investigational products.

It was planned that approximately 300 subjects would be screened with the aim of having 250 subjects complete, 100 subjects in each of 2 naproxen treatment groups (naproxen/DPH combination group and naproxen alone group) and 50 subjects in the DPH alone treatment group. The duration of each subject's participation in the study from Screening Visit to the EOT assessment was up to approximately 4 weeks, including a Screening Period of up to 28 days, a Dosing Period of 2 days, and a Follow-up Period of 2-5 days.

Rescue medication (Lortab (hydrocodone 5mg/APAP 500mg) was allowed if pain intensity was not reduced and adequate pain relief was not achieved any time after administration of study drug, although subjects were encouraged to wait 60 minutes. In

cases of extreme pain, the investigator could administer appropriate analgesics. Pain assessments were completed immediately prior to first rescue use.

The study population consisted of healthy male and females ages 12 years and above with impacted third molars, who were scheduled to undergo surgical removal of a minimum of two third molars, at least one of which had to be a mandibular third molar. Subjects had moderate to severe postoperative pain on a categorical pain rating scale, and a score of at least 50mm on a 100-mm pain severity VAS. Subjects with serious sleep disorders that did not respond to OTC treatment and required a prescription hypnotic or sedative were excluded. Subjects were also excluded if they were receiving any analgesic.

A total of 267 subjects were randomized, all of whom were included in the efficacy and safety assessments. Subjects were randomized to the following treatment groups. Tablets were overencapsulated to maintain the blind.

- Naproxen /DPH combination: naproxen 440mg/ DPH 25mg as 1 naproxen 220mg/DPH 25mg + 1 naproxen 220mg (n=107)
- Naproxen 440mg as 2 naproxen 220mg (n=106)
- DPH 50mg as 2 DPH 25mg (n=54)

Subjects were awakened after 10 hours of sleep if they did not awaken spontaneously.

The primary efficacy parameters, sleep and wakefulness, were measured by actigraphy, and were used to determine time spent awake after sleep onset (WASO; naproxen/DPH vs. naproxen alone) and sleep latency (naproxen/DPH vs. DPH alone).

Secondary objective sleep variables obtained by actigraphy were total sleep time and sleep efficiency. Subjective secondary sleep variables included a Global Assessment of Investigational Product as a Sleep-Aid, Subjective Sleep Questionnaire, and Karolinska Sleep Diary.

Secondary pain variables were similar to those in the Phase 2 and Phase 3 studies above (see complete description of endpoints in Phase 2 study section) and included change from baseline in 4-point categorical pain rating scale, 5-point categorical pain relief scale, time to analgesic rescue medication, cumulative proportion of subject taking rescue medication by hour, and Global Assessment of Investigational Product as a Pain Reliever.

The ITT population (randomized, received study drug, and had at least one efficacy assessment) was used for efficacy analyses. The primary endpoint, WASO and sleep latency, was analyzed using a hierarchical testing procedure in order to protect the overall Type 1 error at the 0.05 level. There was no adjustment for multiple endpoints for secondary endpoint analyses.

## Results

The ITT population was comprised of all 267 randomized subjects, as they all received treatment and had at least one efficacy assessment.

Demographic characteristics were generally comparable among treatment groups. The mean age was 21 years, ranging from 12 to 49 years, 65% of the subjects were female, and 88% were white. Overall, 60% of subjects rated their baseline pain as moderate and 40% severe. The mean VAS pain score at baseline was 76/100mm, and was comparable among treatment groups.

#### *Primary endpoints*

For WASO, the difference between the naproxen 440mg/DPH 25mg group and the naproxen 440mg group was not statistically significant ( $P = 0.3047$ ).

For sleep latency, the difference between the naproxen 440mg/DPH 25mg group and the DPH 50mg group was not statistically significant ( $P = 0.1677$ ).

#### *Secondary sleep endpoints*

For both total sleep time and sleep efficiency, there was no statistically significant difference between the naproxen 440mg/DPH 25 mg group and the naproxen 440 mg group. Naproxen sodium 440mg/DPH 25mg showed improvement over either single ingredient alone in some of the subjective sleep assessments.

#### *Secondary pain endpoints*

Secondary endpoint analyses for pain severity assessments were analyzed using an ANCOVA model. If a subject took rescue medication, the worst score before rescue medication administration was carried forward to the morning score. Time to rescue medication was estimated using the Kaplan Meier method and logrank test for pairwise comparisons. There was no correction of the secondary endpoint analyses for multiple endpoints, therefore the Applicant's p-values are merely descriptive in this setting.

Refer to the section of this review for Study 14837 for a description of the pain assessments (pain intensity, pain relief, global assessment, and rescue medication use), which were the same in both studies.

#### Pain intensity

Pain intensity was collected on a 4-point Categorical Pain Rating Scale, where 0 = no pain and 3 = severe pain. The naproxen 440mg/DPH 25mg and naproxen 440mg treatment groups reported reductions in pain intensity from baseline (median reduction of 1.0 point for each group). The DPH 50mg group had no median reduction in pain intensity from baseline. Mean change from baseline values correlated to the median values, with mean reductions of 1.2 points, 1.1 points, and 0.5 points in the Naproxen 440mg/DPH 25mg group, the naproxen 440mg group, and the DPH 50mg group. A significantly greater reduction in pain intensity occurred in the naproxen 440mg/DPH 25 mg group compared with the DPH 50mg group ( $P < 0.0001$ ). There were no other significant effects.

**Table 18 Summary of Pain Intensity and Change from Baseline (Intent-to-Treat Population)**

Visit	Statistic	Treatment Group		
		NP 440 mg/ DPH 25 mg N = 107	NP 440 mg N = 106	DPH 50 mg N = 54
Day 1 (Baseline)	Mean	2.4	2.4	2.5
	Standard deviation	0.48	0.49	0.50
	Median	2.0	2.0	2.0
	Minimum	2	2	2
	Maximum	3	3	3
Postbaseline	Mean	1.2	1.3	2.0
	Standard deviation	0.92	1.02	0.89
	Median	1.0	1.0	2.0
	Minimum	0	0	0
	Maximum	3	3	3
Change from Baseline	Mean	-1.2	-1.1	-0.5
	Standard deviation	0.87	0.90	0.79
	Median	-1.0	-1.0	0.0
	Minimum	-3	-3	-3
	Maximum	0	0	0

DPH = diphenhydramine hydrochloride; N = number of subjects in the Intent-to-Treat Population;  
NP = naproxen sodium.

0 = No Pain, 1 = Mild Pain, 2 = Moderate Pain, and 3 = Severe Pain.

Negative changes from baseline imply a reduction in pain intensity from baseline.

If rescue medication was taken, the worst score prior to rescue including baseline was carried forward to the morning score and used for analysis.

Source: Study report, p. 64

### Pain relief

In the analysis of pain relief, the overall median response for the naproxen 440mg/DPH 25mg group and naproxen 440mg group was 3.0, corresponding to a rating of “a lot of relief” on the 0 to 4 scale (where 0 = no relief and 4 = complete relief). The DPH 50mg group had a median response of 0.0. These results were also supported by mean values that correlated to the median values, with mean responses of 2.3, 2.2, and 0.9 for the naproxen 440mg/DPH 25mg group, naproxen 440mg group, and DPH 50mg group, respectively. The naproxen 440mg/DPH 25mg group had significantly greater pain relief compared with the DPH 50mg. There were no other significant effects.

**Table 21 Summary of Pain Relief Scale Results (Intent-to-Treat Population)**

Pain Relief Scale Parameter	Treatment Group					
	NP 440 mg/ DPH 25 mg N = 107		NP 440 mg N = 106		DPH 50 mg N = 54	
	n	(%)	n	(%)	n	(%)
Number of subjects included in the analysis	107		106		54	
0 = No relief	24	(22.4)	30	(28.3)	35	(64.8)
1 = A little relief	5	(4.7)	3	(2.8)	4	(7.4)
2 = Some relief	10	(9.3)	15	(14.2)	5	(9.3)
3 = A lot of relief	47	(43.9)	37	(34.9)	8	(14.8)
4 = Complete relief	21	(19.6)	21	(19.8)	2	(3.7)
Mean	2.3	2.2	0.9			
Standard deviation	1.44	1.52	1.29			
Median	3.0	3.0	0.0			
Minimum	0	0	0			
Maximum	4	4	4			

DPH = diphenhydramine hydrochloride; N = number of subjects in the Intent-to-Treat Population;  
NP = naproxen sodium.

If rescue medication was taken, the score of 0 (no relief) was used for the morning's rating of pain relief.

Study report, P. 66

### Global assessment

In the analysis of the Global Assessment of Investigational Product as a Pain Reliever, the overall median response for the naproxen 440mg/DPH 25mg group, the naproxen 440mg group, and the DPH 50mg group was 3.0, corresponding to a rating of "very good" on the 0 to 4 scale (where 0 = poor and 4 = excellent). The mean values differed more between the naproxen treated and DPH treated groups compared to the median values, with mean responses of 2.8, 2.7, and 2.2 for the naproxen 440mg/DPH 25mg group, the naproxen 440mg group, and the DPH50mg group, respectively. The difference between the naproxen 440mg/DPH 25mg group and the DPH50 mg group was significant. No other significant differences were observed.

**Table 23 Analysis of Global Assessment of Investigational Product as a Pain Reliever: Summary (Intent-to-Treat Population)**

Response	Treatment Group					
	NP 440 mg/ DPH 25 mg N = 107		NP 440 mg N = 106		DPH 50 mg N = 54	
	n	(%)	n	(%)	n	(%)
Number of subjects included in the analysis	85		79		19	
0 = Poor	1	(0.9)	1	(0.9)	1	(1.9)
1 = Fair	4	(3.7)	3	(2.8)	5	(9.3)
2 = Good	22	(20.6)	25	(23.6)	3	(5.6)
3 = Very good	40	(37.4)	38	(35.8)	9	(16.7)
4 = Excellent	18	(16.8)	12	(11.3)	1	(1.9)
Mean	2.8	2.7	2.2			
Standard deviation	0.86	0.82	1.08			
Median	3.0	3.0	3.0			
Minimum	0	0	0			
Maximum	4	4	4			

DPH = diphenhydramine hydrochloride; N = number of subjects in the Intent-to-Treat Population;

Source: Study report p. 67

#### Rescue medication use

The cumulative proportion of subjects taking rescue medication was calculated as the number of subjects who had taken rescue medication at a given time divided by the number subjects treated.

By 180 minutes postdose, half of the subjects (53.7%) took rescue medication in the DPH 50 mg group compared to 13.1% and 12.3% in the naproxen 440mg/DPH 25mg and naproxen 440mg groups, respectively. By 600 minutes postdose, the DPH 50mg group had the highest proportion of subjects taking rescue medication (64.8%) compared to the naproxen 440mg/DPH 25mg (22.4%) and naproxen 440mg groups (28.3%).

**Table 13 Cumulative Proportion of Subjects Taking Rescue Medication (Safety Population)**

Time After Dosing That Rescue Medication Was Taken	Treatment Group					
	NP 440 mg/ DPH 25 mg N = 107		NP 440 mg N = 106		DPH 50 mg N = 54	
	n	(%)	n	(%)	n	(%)
≤ 60 minutes	0		1	(0.9)	0	
≤ 120 minutes	9	(8.4)	12	(11.3)	21	(38.9)
≤ 180 minutes	14	(13.1)	13	(12.3)	29	(53.7)
≤ 240 minutes	15	(14.0)	17	(16.0)	32	(59.3)
≤ 300 minutes	16	(15.0)	23	(21.7)	33	(61.1)
≤ 360 minutes	17	(15.9)	25	(23.6)	34	(63.0)
≤ 420 minutes	21	(19.6)	26	(24.5)	35	(64.8)
≤ 480 minutes	22	(20.6)	28	(26.4)	35	(64.8)
≤ 540 minutes	24	(22.4)	30	(28.3)	35	(64.8)
≤ 600 minutes	24	(22.4)	30	(28.3)	35	(64.8)

DPH = diphenhydramine hydrochloride; NP = naproxen sodium; N = number of subjects treated in the Safety Population

Source: Study report, p. 58

The Kaplan-Meier analysis of time to rescue medication is summarized for the ITT Population in the Applicant's table and graph below.

Table 14.2.2a  
Kaplan-Meier Analysis of Sleep Latency  
(ITT Population)

Statistics	Treatment Group			P-value [a]
	NP 440 mg/ DPH 25 mg N=107	NP 440 mg N=106	DPH 50 mg N=54	
Number of Subjects Included in Analysis	107	106	54	
Number of Subjects Censored	4	2	5	
Median Time (Minutes)	23.50	16.75	27.50	
95% CI (Minutes)	(18.00, 28.00)	(13.50, 25.00)	(16.00, 36.50)	
Comparison NP 440 mg/DPH 25 mg versus DPH 50 mg				0.1677

[a] P-value from log rank test.

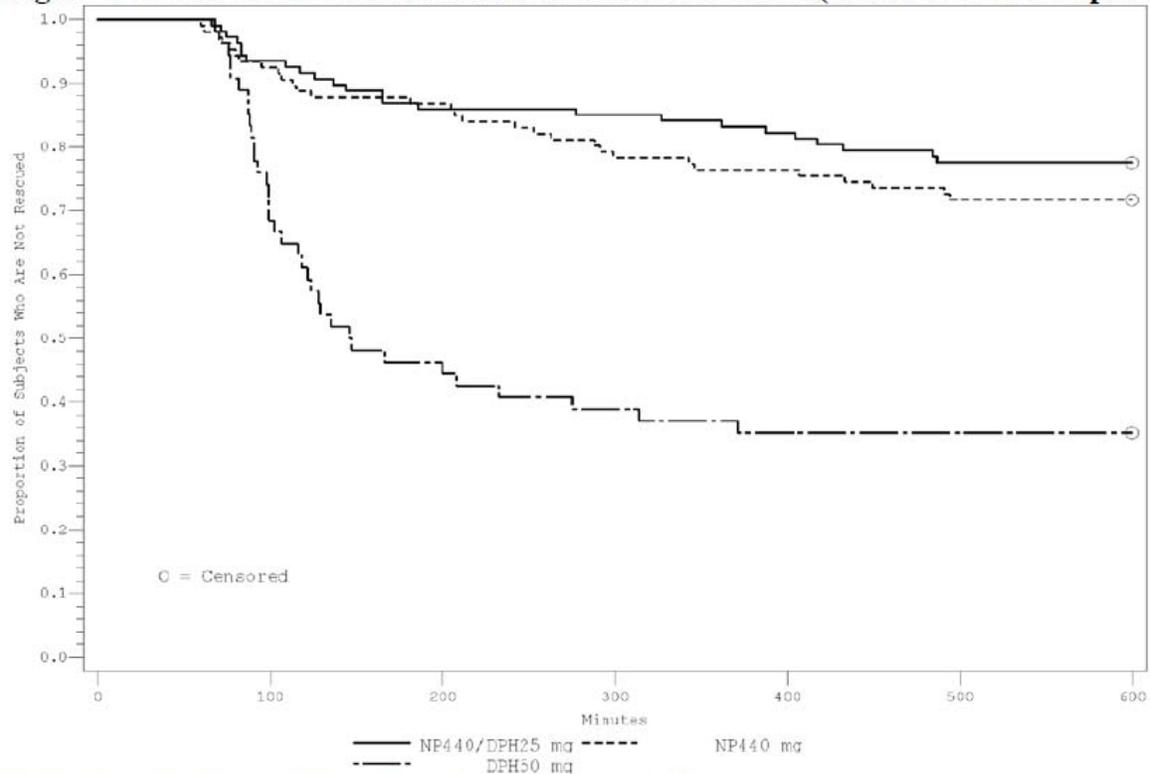
Note: N = Number of subjects in the ITT Population.

Note: All measurements are in minutes.

NP: Naproxen Sodium DPH: Diphenhydramine Hydrochloride ITT: Intent-to-Treat Population

Source: Study report, p. 119

**Figure 4 Box Plot for Time to Rescue Medication Taken (Intent-to-Treat Population)**



DPH = diphenhydramine hydrochloride; NP = naproxen sodium.

Source: Study report, p. 69

The number of times subjects took rescue is summarized below.

Table 14.2.13  
Number of Times Subjects Took Rescue Medication  
(ITT Population)

Number of Times Subjects Took Rescue Medication	Treatment Group		
	NP 440 mg/ DPH 25 mg N=107 n (%)	NP 440 mg N=106 n (%)	DPH 50 mg N=54 n (%)
0	83 ( 77.6)	76 ( 71.7)	19 ( 35.2)
1	22 ( 20.6)	29 ( 27.4)	28 ( 51.9)
2	2 ( 1.9)	1 ( 0.9)	7 ( 13.0)

Note: N = Number of subjects in the ITT Population.

NP: Naproxen Sodium DPH: Diphenhydramine Hydrochloride ITT: Intent-to-Treat Population

Source: Study report, p. 155

The majority of subjects in the two naproxen groups did not take any analgesic rescue medication (98-99%), while the majority of subjects in the DPH group (87%) took at least one dose of rescue medication.

### Discussion

According to the Applicant's analyses, the primary efficacy results demonstrated that the combination of naproxen 440mg/DPH 25mg did not provide a statistically significant improvement for WASO or sleep latency over naproxen 440mg alone and DPH 25mg alone respectively. The secondary sleep endpoints supported the findings of the primary analyses.

In terms of pain, the chosen endpoints and the timing of assessments appear appropriate for measurements of analgesia in a combination sleep/analgesic product. The pain endpoints in this study do support that naproxen in this combination is an analgesic, however, the value of the pain endpoint analyses is limited by the fact that the study failed in terms of the primary endpoint.

### **Overall Conclusions**

The Applicant conducted one Phase 2 pilot efficacy study and two Phase 3 key efficacy studies. According to the Applicant the results from Study 14837 demonstrated that the combination naproxen sodium 440mg/DPH 50mg is superior to its individual components in terms of the primary endpoints (WASO and sleep latency). Lower doses of both ingredients in the combination product were evaluated, naproxen 220mg/DPH 50mg in Study 14837, and naproxen sodium 440mg/DPH 25mg in Study 15881. Both of these dose combinations failed demonstrate superiority over their individual components. Of note, in Study 15881, the combination was compared to naproxen sodium 440mg alone and DPH 50mg alone, rather than 25mg, the amount in the combination.

The analgesic assessments conducted in the three efficacy studies, pain intensity, pain relief, global impression of the product as a pain reliever, amount of rescue and proportion of subjects using analgesic rescue, were appropriate. The timing of these assessments was also adequate. Because the intended use of the combination product is a sleep aid for patients who cannot sleep due to pain, assessments were conducted prior to sleep onset, on morning waking, and at the time of request for rescue medication. In a typical analgesic study, pain scores would be captured more frequently.

Because the pain assessments were collected as secondary endpoints and no adjustment was made in the statistical analysis plan to control for Type 1 error, these results are descriptive in nature. That said, the results were consistent among the three studies and showed that naproxen in combination with DPH acts as an analgesic, and in general, a dose response in terms of analgesia was shown for naproxen 440mg compared to naproxen 220mg when administered in combination with DPH. In all studies, naproxen, at doses of 440mg and 220mg, in combination with DPH (25mg or 50mg), demonstrated numerically similar or slightly superior analgesia compared to naproxen alone at the same doses. DPH alone demonstrated little to no analgesic efficacy.

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/s/  
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ELLEN W FIELDS  
10/18/2013

SHARON H HERTZ  
10/18/2013  
Signing for myself and Bob Rappaport, M.D.

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology  
Office of Medication Error Prevention and Risk Management**

**Label, Labeling and Packaging Review**

Date: September 26, 2013

Reviewer: Chi-Ming (Alice) Tu, PharmD  
Division of Medication Error Prevention and Analysis

Team Leader: Todd Bridges, RPh  
Division of Medication Error Prevention and Analysis

Drug Name and Strength: Aleve PM (Naproxen Sodium and Diphenhydramine HCl),  
220 mg/25 mg

Application Type/Number: NDA 205352

Submission Number: 1

Applicant/Sponsor: Bayer

OSE RCM #: 2013-788

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## 1 INTRODUCTION

This review evaluates the proposed container labels and carton labeling for Aleve PM (Naproxen Sodium/Diphenhydramine HCl), NDA 205352 for areas of vulnerability that could lead to medication errors.

### 1.1 REGULATORY HISTORY

Aleve (Naproxen Sodium) Tablets, 220 mg, was approved on January 11, 1994 under NDA 020204. Aleve-D (Naproxen Sodium/ Pseudoephedrine HCl) Extended-release Tablets, 220 mg/120 mg, was approved on November 29, 1999 under NDA 021076.

Products currently marketed among the Aleve produce line are shown in Table 1.

**Table 1.** Aleve Product Line (Information retrieved from <http://aleve.com/products.php> and <http://aleved.com/products/>, accessed on April 8, 2013).

Product Name (Descriptor, when applicable)	Dosage Form	Active Ingredient(s)	Strength(s)	Application #
Aleve	Tablets	Naproxen Sodium	220 mg	NDA 020204
Aleve	Caplets			
Aleve	Gelcaps			
Aleve	Liquid Gels			
Aleve-D Sinus & Cold	Caplets	Naproxen Sodium/ Pseudoephedrine HCl	220 mg/ 120 mg	NDA 021076
(b)(4)	Caplets			

The Applicant is now seeking to add Aleve PM\*\*\* (Naproxen Sodium/Diphenhydramine HCl) Tablets, 220 mg/25 mg, to the Aleve product line. Additionally, the Applicant (b)(4) NDA 200364, (b)(4) (Naproxen Sodium) Tablets, 660 mg (b)(4)

## 1.2 PRODUCT INFORMATION

The following product information is provided in the March 20, 2013 submission.

<p><b>Drug Facts</b></p> <p><b>Active ingredients Purposes (in each caplet)</b> Diphenhydramine hydrochloride 25 mg.....Nighttime sleep-aid Naproxen sodium 220 mg (naproxen 200 mg) (NSAID)*....Pain reliever *nonsteroidal anti-inflammatory drug</p> <p><b>Uses</b></p> <ul style="list-style-type: none"><li>for relief of occasional sleeplessness when associated with minor aches and pains</li><li>helps you fall asleep and stay asleep</li></ul> <p><b>Warnings</b></p> <p>Allergy alert: Naproxen sodium may cause a severe allergic reaction, especially in people allergic to aspirin. Symptoms may include:</p> <ul style="list-style-type: none"><li>hives</li><li>facial swelling</li><li>asthma (wheezing)</li><li>shock</li><li>skin reddening</li><li>rash</li><li>blisters</li></ul> <p>If an allergic reaction occurs, stop use and seek medical help right away.</p> <p><b>Stomach bleeding warning:</b> This product contains an NSAID, which may cause severe stomach bleeding. The chance is higher if you:</p> <ul style="list-style-type: none"><li>are age 60 or older</li><li>have had stomach ulcers or bleeding problems</li><li>take a blood thinning (anticoagulant) or steroid drug</li><li>take other drugs containing prescription or nonprescription NSAIDs (aspirin, ibuprofen, naproxen, or others)</li><li>have 3 or more alcoholic drinks every day while using this product</li><li>take more or for a longer time than directed</li></ul> <p><b>Do not use</b></p> <ul style="list-style-type: none"><li>if you have ever had an allergic reaction to any other pain reliever/fever reducer</li><li>unless you have time for a full night's sleep</li><li>in children under 12 years of age</li></ul>	<p><b>Drug Facts (continued)</b></p> <ul style="list-style-type: none"><li>right before or after heart surgery</li><li>with any other product containing diphenhydramine, even one used on skin</li><li>if you have sleeplessness without pain</li></ul> <p><b>Ask a doctor before use if</b></p> <ul style="list-style-type: none"><li>stomach bleeding warning applies to you</li><li>you have problems or serious side effects from taking pain relievers or fever reducers</li><li>you have a history of stomach problems, such as heartburn</li><li>you have high blood pressure, heart disease, liver cirrhosis, kidney disease, or asthma</li><li>you are taking a diuretic</li><li>you have a breathing problem such as emphysema or chronic bronchitis</li><li>you have glaucoma</li><li>you have trouble urinating due to an enlarged prostate gland</li></ul> <p><b>Ask a doctor or pharmacist before use if you are</b></p> <ul style="list-style-type: none"><li>taking sedatives or tranquilizers, or any other sleep-aid</li><li>under a doctor's care for any serious condition</li><li>taking any other antihistamines</li><li>taking any other drug</li></ul> <p><b>When using this product</b></p> <ul style="list-style-type: none"><li>drowsiness will occur</li><li>avoid alcoholic drinks</li><li>do not drive a motor vehicle or operate machinery</li><li>take with food or milk if stomach upset occurs</li><li>the risk of heart attack or stroke may increase if you use more than directed or for longer than directed</li></ul> <p><b>Stop use and ask a doctor if</b></p> <ul style="list-style-type: none"><li>you experience any of the following signs of stomach bleeding:<ul style="list-style-type: none"><li>feel faint</li><li>vomit blood</li><li>have bloody or black stools</li><li>have stomach pain that does not get better</li></ul></li><li>pain gets worse or lasts more than 10 days</li><li>sleeplessness persists continuously for more than 2 weeks. Insomnia may be a symptom of a serious underlying medical illness.</li><li>redness or swelling is present in the painful area</li><li>any new symptoms appear</li><li>you have difficulty swallowing</li><li>it feels like the pill is stuck in your throat</li></ul> <p>If pregnant or breast-feeding, ask a health professional before use. It is especially important not to use naproxen sodium during the last 3 months of pregnancy unless definitely directed to do so by a doctor because it may cause problems in the unborn child or complications during delivery. Keep out of reach of children. In case of overdose, get medical help or contact a Poison Control Center right away.</p>	<p><b>Drug Facts (continued)</b></p> <p><b>Directions</b></p> <ul style="list-style-type: none"><li>do not take more than directed</li><li>drink a full glass of water with each dose</li><li>adults and children 12 years and over: take 2 caplets at bedtime</li><li>do not take more than 2 caplets in 24 hours</li><li>if taken with food, this product may take longer to work</li></ul> <p><b>Other information</b></p> <ul style="list-style-type: none"><li>read all warnings and directions before use</li><li>each caplet contains: sodium 20 mg</li><li>store at 20-25°C (68-77°F)</li><li>avoid high humidity and excessive heat above 40°C (104°F)</li></ul> <p><b>Inactive ingredients</b> carnauba wax, FD&amp;C blue #2 aluminum lake, hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, povidone, purified water, talc, titanium dioxide</p> <p><b>Questions or comments?</b> 1-800-395-0689 (Mon – Fri 9AM – 5PM EST) (b) (4)</p> <p style="text-align: center;">Bayer</p>
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- How supplied: 2-count pouch, and 20-, 40- and 80-count bottles, packaged in cartons.

## 2 METHODS AND MATERIALS REVIEWED

DMEPA searched the FDA Adverse Event Reporting System (FAERS) database for Aleve medication error reports. We also reviewed the Aleve PM container labels and carton labeling submitted by the Applicant.

## 2.1 SELECTION OF MEDICATION ERROR CASES

We searched FAERS using the strategy listed in Table 2. The date of the search was limited from February 14, 2013, the date of our last search in OSE Review #2013-34, to the search date of April 8, 2013.

<b>Table 2: FAERS Search Strategy on April 8, 2013</b>	
Date	2/14/2013 – 4/8/2013
Product Names	Aleve
MedDRA Search Strategy	Medication Errors (HLGT) Product Labeling Issues (HLT) Product Packaging Issues (HLT) Product Quality Issues NEC (HLT)

The FAERS search identified 275 cases. Each case was reviewed for relevancy and duplication. After individual review, 104 cases were not included in the final analysis for the following reasons:

- Cases of intentional misuse, attempted self-harm or suicide.
- Cases of accidental child ingestions.
- Cases reporting adverse events unrelated to medication errors.
- Cases related to the use of expired drug products.
- Cases complaining lack of drug efficacy.
- Cases of medication errors associated with another drug product.
- Cases of off-label prescribed use.
- Cases lacking adequate narrative detail for determination of a medication error.

## 2.2 LITERATURE SEARCH

We searched PubMed and the ISMP publications for “Aleve” September 6, 2013 for additional cases and actions concerning Aleve, but our search did not identify any relevant finding.

## 2.3 LABELS AND LABELING

Using the principles of human factors and Failure Mode and Effects Analysis,<sup>1</sup> along with post marketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Container Labels submitted March 20, 2013 (Appendix B)
- Carton Labeling submitted March 20, 2013 (Appendix C)

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<sup>1</sup> Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

## 2.4 PREVIOUSLY COMPLETED REVIEWS

DMEPA had previously completed the following reviews related to Aleve:

- 2009-1987 (b) (4) proprietary name review,
- 2009-2443 (b) (4) labels and labeling review,
- 2013-34 (b) (4) labels, labeling and packaging review,
- 2013-911 (b) (4) proprietary name review, and
- 2013-787 Aleve PM proprietary name review.

We looked at the reviews related to labels and labeling to ensure our past recommendations are also considered for this review if applicable.

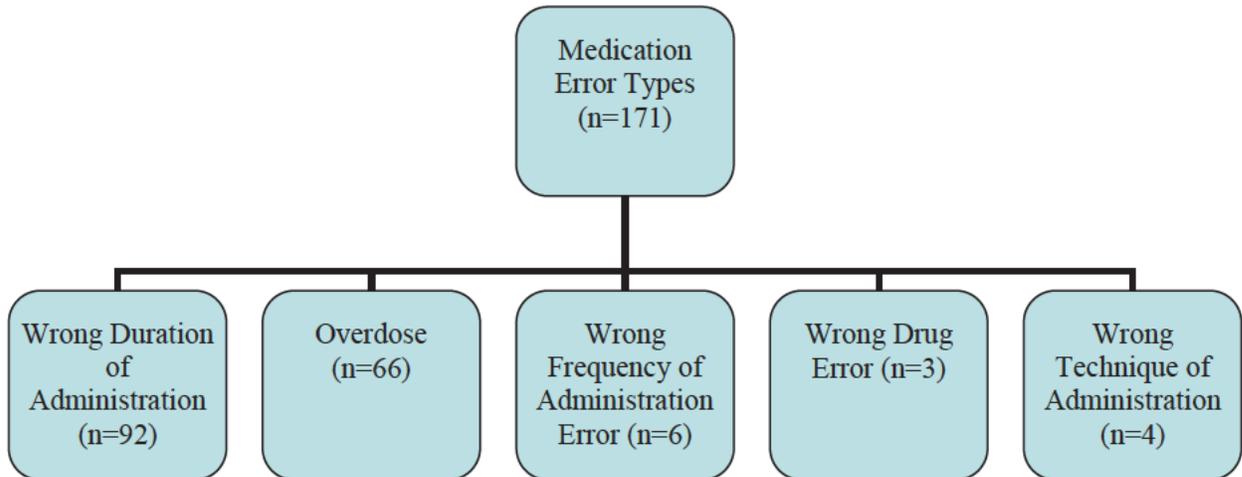
## 3 MEDICATION ERROR RISK ASSESSMENT

The following sections describe the results of our FAERS search and the risk assessment of the Aleve product design as well as the associated labels and labeling.

### 3.1 MEDICATION ERROR CASES

Following exclusions as described in section 2.1, 171 Aleve medication error cases remained for our detailed analysis. The NCC MERP Taxonomy of Medication Errors was used to code the type and factors contributing to the errors when sufficient information was provided by the reporter<sup>2</sup>. Figure 1 provides a stratification of the number of cases included in the review by type of error. Appendix D provides listings of all case numbers for the cases summarized in this review.

**Figure 1: Aleve medication errors (n = 171) categorized by type of error**



<sup>2</sup> The National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) Taxonomy of Medication Errors. Website <http://www.nccmerp.org/pdf/taxo2001-07-31.pdf>. Accessed June 1, 2011.

#### Wrong Duration of Administration Error (n=92)

Ninety-two cases of wrong duration medication errors, where consumers took the Aleve product for longer than 10 days, were reported. The root cause of the errors was not reported. The outcomes of the errors were: not reported (n=61), lack of effect (n=4), adverse events such as stomachache, constipation, diarrhea, dizziness/nausea, nosebleed, or itching (n=21); blood in stool (n=3), cough up blood (n=1), kidney failure (n=1), and “constricts his blood vessels, it almost killed him” (n=1).

#### Overdose (n=66)

Sixty-six cases of Aleve overdose medication errors were reported. The cases either did not provide the reason for the overdose or stated the consumers took more Aleve because they forgot they had already taken a dose earlier. The outcomes were not reported in 40 out of the 66 cases. For those cases where outcomes were reported, the outcomes ranged from no adverse events to adverse events such as “bled out and nearly died” (n=1), vomiting, stomachache and spit up blood (n=1), gastrointestinal (GI) ulcer with decreased hemoglobin (n=1), or bleeding GI ulcer and hospitalization (n=2).

#### Wrong Frequency of Administration Error (n=6)

Six cases of wrong frequency of administration errors where the next dose was administered too soon were reported. The root cause was either not described in the case narrative or reported as the consumer took another dose too soon due to lack of adequate pain relief. The outcomes were not reported in three cases, and reported as diarrhea (n=1), uncomfortable (n=1), or vomiting (n=1) in the remaining three cases.

#### Wrong Drug Error (n=3)

Three cases of wrong drug medication errors were reported. All three case narratives described the consumer intended to take Ibuprofen or Motrin, but took Aleve by mistake with no further details provided. The outcomes of the wrong drug errors were not reported in all three cases.

#### Wrong Technique of Administration (n=4)

Four cases of wrong technique of administration medication errors were reported. Two of the four cases described consumers sucking on the Aleve and experienced burning of the tongue or throat. One case described taking Aleve without water, and the consumer experienced the pill lodged in throat. The last case reported the consumer took Aleve with alcohol and complained about the lack of drug effect. The root cause was not provided in case narratives.

### **3.2 INTEGRATED SUMMARY OF MEDICATION ERROR RISK ASSESSMENT**

Overdoses and extended duration of product use by consumers for longer than 10 days are common among OTC pain reliever products (i.e., Tylenol, Motrin, and Advil). Each of these OTC pain reliever products is labeled with their respective proper dosage and administration in the Drug Facts, and all of them contain the statement “Stop use and ask a doctor if pain gets worse or lasts more than 10 days” in the Drug Facts. The proposed Aleve PM container labels and carton labeling are also labeled with its proper dosage and

administration (i.e., 2 caplets at bedtime, drink a full glass of water with each dose, etc.) as well as the same “Stop use...10 days” statement.

Regarding the wrong frequency of administration errors identified for existing Aleve products, the modifier PM in the proposed Aleve PM product is meant to convey its intended nighttime use (administered only before bedtime), which is consistent with other OTC pain reliever/ nighttime sleep aid products (i.e., Advil PM, Excedrin PM, Motrin PM, and Tylenol PM). Thus, we will not recommend any additional labeling statements at this time.

Our review of the container labels and carton labeling found the following (See Appendices B and C):

- The proprietary name is presented in two different cases, font sizes and colors.
- The plus symbol in the statement “Sleep aid + 12 hour pain relieving strength of Aleve”.

The “ALEVE” portion of the proprietary name is presented in all uppercase letters on the labels and labeling (See Appendix B and C). Although DMEPA typically requests the proprietary name to be presented in title case, all of the existing products in Aleve product line are marketed with the product name in yellow colored uppercase letters. Given that we are not aware of any safety issues related to such presentation of the Aleve name, in this case, we will not request the Applicant to change the presentation of the root name Aleve to title case.

The proposed container labels and carton labeling do not present the entire proprietary name “ALEVE pm” in equal prominence. The Applicant uses all lower case and blue font for “pm” to draw attention to the difference between the proprietary name of this proposed product and the existing Aleve products, similar to the method utilized for the “Aleve-D” product line where “D” (representing Pseudoephedrine HCl) is presented in red (Image not shown. See Table 1 in Section 1.1 for Aleve product line). Since the proposed product is also a multi-ingredient product containing Diphenhydramine in addition to Naproxen and is dosed only at bedtime, it appears reasonable to present the modifier “pm” in a different prominence and color compared to the root name to help consumers in correct product selection. In addition, other OTC Pain Reliever/ Nighttime Sleep Aid products currently marketed also utilize different cases, font sizes and colors to present the proprietary name (See Figure 2).

Additionally, existing Aleve (Naproxen Sodium, 220 mg) products already contain the statement “Strength to last 12 hours” on the principal display panel, however, the plus symbol (+) is a new addition to the proposed labels and labeling. The plus symbol is an error prone symbol that has been mistaken for the number “4” in post-marketing use, thus should be avoided.<sup>2</sup>

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<sup>2</sup> Institute for Safe Medication Practices (ISMP). ISMP’s List of Error-prone abbreviations, symbols, and dosage designations. <http://www.ismp.org/Tools/errorproneabbreviations.pdf>

**Figure 2.** Carton Labeling of Other OTC Pain Reliever/ Nighttime Sleep Aids



#### 4 CONCLUSIONS AND RECOMMENDATIONS

Based on this review, DMEPA recommends the following be implemented prior to approval of this NDA. If you have questions or need clarifications, please contact Abiola Olagundoye, OSE Safety Regulatory Project Manager, at 301-796-3982.

A. Comments to the Division

1. DMEPA identified two medication error cases related to consumers sucking on Aleve (instead of swallowing the tablet whole) and experiencing burning of the tongue or throat. We defer to the Division as to whether a statement such as “Swallow whole. Do not chew or crush caplets” should be added to the Directions of this product, and to applicable existing Aleve product labels and labeling at next printing.

B. Comments to the Applicant

1. Container Labels and Carton Labeling

- a. Remove the symbol “+” from the PDP and spell out its intended meaning (i.e., “plus”). The plus symbol is an error prone symbol that has been mistaken for the number “4”.<sup>3</sup>

<sup>3</sup> Institute for Safe Medication Practices (ISMP). ISMP’s List of Error-prone abbreviations, symbols, and dosage designations. <http://www.ismp.org/Tools/errorproneabbreviations.pdf>

## **APPENDICES**

### **Appendix A. Database Descriptions**

#### **FDA Adverse Event Reporting System (FAERS)**

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The informatics structure of the database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FDA implemented FAERS on September 10, 2012, and migrated all the data from the previous reporting system (AERS) to FAERS. Differences may exist when comparing case counts in AERS and FAERS. FDA validated and recoded product information as the AERS reports were migrated to FAERS. In addition, FDA implemented new search functionality based on the date FDA initially received the case to more accurately portray the follow up cases that have multiple receive dates.

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

**Appendix B:** Container Labels

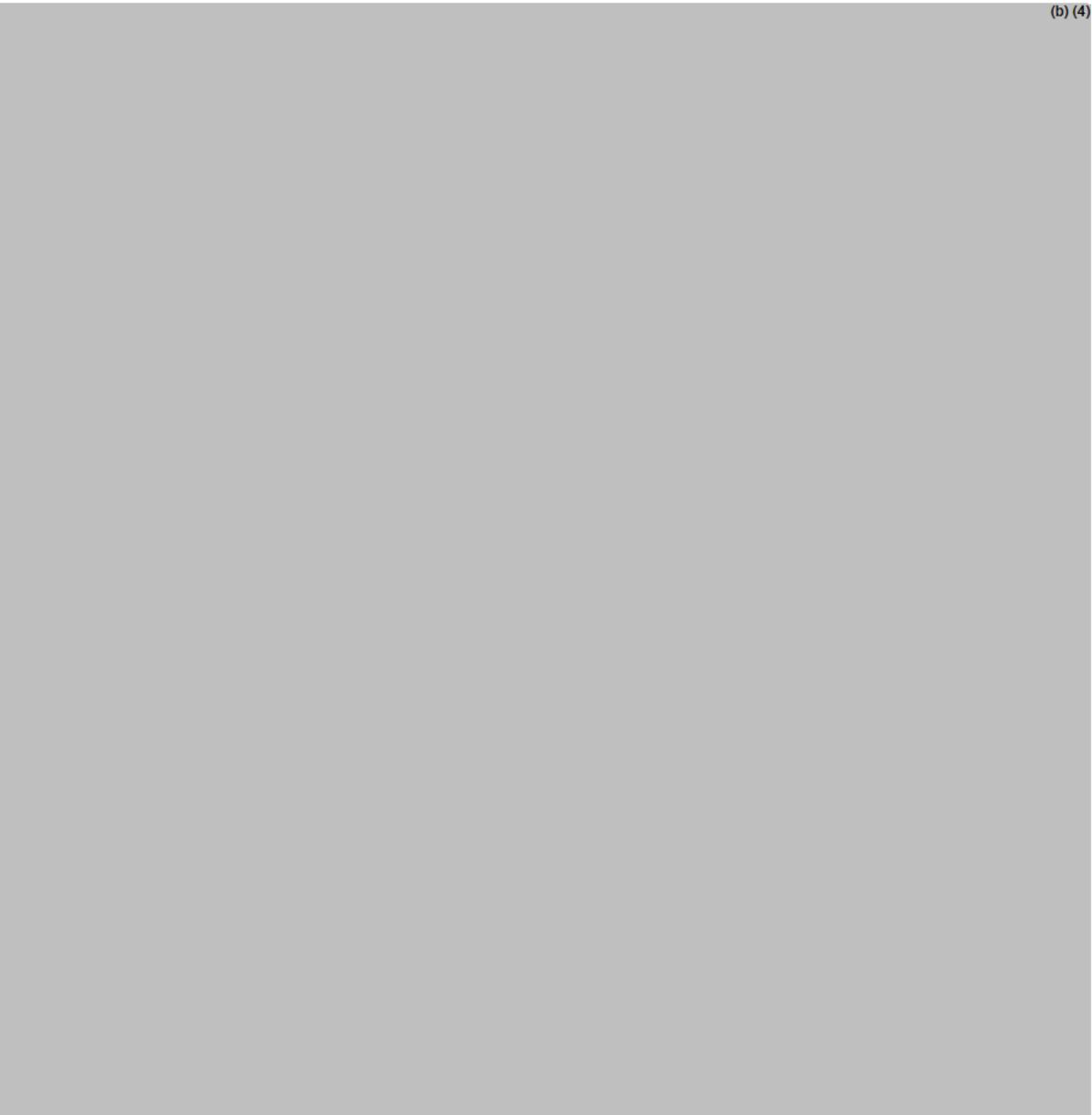
Only the 40-count packaging configuration is shown here. See submission for all packaging configurations (2, 20, and 80 count).



**Appendix C:** Carton Labeling

Only the 40-count packaging configuration is shown here. See submission for all packaging configurations (2, 20, and 80 count).

(b) (4)



**Appendix D: Case numbers discussed in this review**

FAERS Case #	Version Number	Manufacturer Control #	FAERS Case #	Version Number	Manufacturer Control #
9135264	1	US-BAYER-2013-020673	9110103	1	US-BAYER-2013-015773
9137355	1	US-BAYER-2013-026995	9116435	1	US-BAYER-2013-023608
9122921	1	US-BAYER-2013-023045	9116439	1	US-BAYER-2013-023481
9101398	1	US-BAYER-2013-018874	9116448	1	US-BAYER-2013-023761
9105884	1	US-BAYER-2013-018879	9116462	1	US-BAYER-2013-023783
9101310	1	US-BAYER-2013-011162	9120005	1	US-BAYER-2013-020478
9115970	1	US-BAYER-2013-023732	9123761	1	US-BAYER-2013-023073
9142873	1	US-BAYER-2013-023757	9126723	1	US-BAYER-2013-024846
9211044	1	US-BAYER-2013-039155	9126729	1	US-BAYER-2013-024892
9184052	1	US-BAYER-2013-035136	9130390	1	US-BAYER-2013-021676
9108152	1	US-BAYER-2013-018238	9135194	1	US-BAYER-2013-026319
9149063	1	US-BAYER-2013-028872	9135253	1	US-BAYER-2013-026733
9188353	1	US-BAYER-2013-036568	9135262	1	US-BAYER-2013-026941
9101743	1	US-BAYER-2013-011195	9135269	1	US-BAYER-2013-021461
9145975	1	US-BAYER-2013-028053	9137926	1	US-BAYER-2013-026834
9177053	1	US-BAYER-2013-035127	9139739	1	US-BAYER-2013-027621
9120991	1	US-BAYER-2013-024896	9140472	1	US-BAYER-2013-025641
9069117	1	US-BAYER-2013-018893	9142839	1	US-BAYER-2013-028085
9101447	1	US-BAYER-2013-016187	9142870	1	US-BAYER-2013-028219
9101740	1	US-BAYER-2013-020517	9142944	1	US-BAYER-2013-028344
9102516	1	US-BAYER-2013-020158	9146075	1	US-BAYER-2013-028704
9104862	1	US-BAYER-2013-019732	9146094	1	US-BAYER-2013-028818
9104863	1	US-BAYER-2013-019732	9146627	1	US-BAYER-2013-028547
9105961	1	US-BAYER-2013-020182	9154110	1	US-BAYER-2013-029843
9106898	1	US-BAYER-2013-015472	9154179	1	US-BAYER-2013-030043
9108150	1	US-BAYER-2013-016335	9157607	1	US-BAYER-2013-030809
9109509	1	US-BAYER-2013-020652	9159747	1	US-BAYER-2013-031348
9123755	1	US-BAYER-2013-022836	9160314	1	US-BAYER-2013-029454
9131275	1	US-BAYER-2013-025974	9162200	1	US-BAYER-2013-031908
9131296	1	US-BAYER-2013-025145	9162201	1	US-BAYER-2013-031730
9133078	1	US-BAYER-2013-025104	9165541	1	US-BAYER-2013-032356
9135215	1	US-BAYER-2013-026309	9168401	1	US-BAYER-2013-033157
9137077	1	US-BAYER-2013-025670	9170801	2	US-BAYER-2013-033697
9140615	1	US-BAYER-2013-027906	9173411	1	US-BAYER-2013-034444
9142847	1	US-BAYER-2013-028176	9174954	1	US-BAYER-2013-035062
9148935	1	US-BAYER-2013-029407	9175151	1	US-BAYER-2013-034872
9149062	1	US-BAYER-2013-029458	9175323	1	US-BAYER-2013-035100
9155912	1	US-BAYER-2013-029974	9177859	1	US-BAYER-2013-035750
9162150	1	US-BAYER-2013-031860	9177980	1	US-BAYER-2013-035653
9162692	1	US-BAYER-2013-031737	9183366	1	US-BAYER-2013-036487
9170817	1	US-BAYER-2013-033684	9184519	1	US-BAYER-2013-036457
9173414	1	US-BAYER-2013-034554	9189725	1	US-BAYER-2013-037509
9176980	1	US-BAYER-2013-035241	9197065	1	US-BAYER-2013-038915
9177841	1	US-BAYER-2013-035394	9202219	1	US-BAYER-2013-041091

9191340	1	US-BAYER-2013-036778	9204469	1	US-BAYER-2013-041343
9201505	1	US-BAYER-2013-039911	9205227	1	US-BAYER-2013-041803
9201582	1	US-BAYER-2013-040145	9206969	1	US-BAYER-2013-041995
9202221	1	US-BAYER-2013-039580	9206974	1	US-BAYER-2013-041700
9204446	1	US-BAYER-2013-041488	9209699	1	US-BAYER-2013-042803
9204458	1	US-BAYER-2013-041464	9215178	1	US-BAYER-2013-043065
9205226	1	US-BAYER-2013-041892	9146143	1	US-BAYER-2013-028772
9209641	1	US-BAYER-2013-042565	9197274	1	US-BANPHARM-20131025
9215172	1	US-BAYER-2013-043174	9189741	1	US-BAYER-2013-037496
9215556	1	US-BAYER-2013-043767	9106604	1	US-BANPHARM-20130683
9193501	2	US-BAYER-2013-038380	9101785	1	US-BAYER-2013-020545
9170828	1	US-BAYER-2013-033638	9189694	1	US-BAYER-2013-037411
9102533	1	US-BAYER-2013-020315	9173405	1	US-BAYER-2013-034578
9139863	1	US-BAYER-2013-026019	9173413	1	US-BAYER-2013-034642
9099325	1	US-BAYER-2013-012513	9105878	1	US-BAYER-2013-021964
9209695	1	US-BAYER-2013-042617	9206984	1	US-BAYER-2013-041269
9177873	2	US-BAYER-2013-033225	9176985	1	US-BAYER-2013-035366
9103851	1	US-BAYER-2013-020215	9135265	1	US-BAYER-2013-026641
9104268	1	US-BAYER-2013-020970	9145948	1	US-BAYER-2013-027982
9101436	1	US-BAYER-2013-019664	9177865	1	US-BAYER-2013-035602
9104267	1	US-BAYER-2013-019600	9160392	1	US-BAYER-2013-030066
9165549	1	US-BAYER-2013-032410	9146029	1	US-BAYER-2013-028829
9144439	1	US-BAYER-2013-028617	9200607	1	US-BAYER-2013-039644
9163512	2	US-PFIZER INC- 2013081212	9157618	1	US-BAYER-2013-029981
9189720	1	US-BAYER-2013-037616	9177051	1	US-BAYER-2013-033263
9209686	1	US-BAYER-2013-042660	9116461	1	US-BAYER-2013-020893
9131321	1	US-BAYER-2013-024114	9122764	1	US-BAYER-2013-020887
9156006	1	US-BAYER-2013-028906	9148991	1	US-BAYER-2013-027465
9207945	1	US-BAYER-2013-039516	9152638	1	US-BAYER-2013-024366
9149040	1	US-BAYER-2013-029165	9174946	1	US-BAYER-2013-034944
9173415	1	US-BAYER-2013-034585	9189662	1	US-BAYER-2013-037634
9149048	1	US-BAYER-2013-026915	9170823	1	US-BAYER-2013-033543
9182813	1	US-BAYER-2013-033840	9135315	1	US-BAYER-2013-026642
9131295	1	US-BAYER-2013-026282	9065966	1	US-BAYER-2013-018137
9157475	1	US-BAYER-2013-030194	9066022	1	US-BAYER-2013-017950
9129182	1	US-BAYER-2013-023756	9099312	1	US-BAYER-2013-018464
9175148	1	US-BAYER-2013-034937	9101467	1	US-BAYER-2013-015814
9190430	1	US-BAYER-2013-033819	9101468	1	US-BAYER-2013-015814
9104259	1	US-BAYER-2013-019288	9101745	1	US-BAYER-2013-020677
9152178	1	US-BAYER-2013-029856	9101777	1	US-BAYER-2013-018634
9108167	1	US-BAYER-2013-021726	9103845	1	US-BAYER-2013-020900
9109462	1	US-BAYER-2013-021566	9108151	1	US-BAYER-2013-022373

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/s/  
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CHI-MING TU  
09/26/2013

TODD D BRIDGES  
09/26/2013

**MEMORANDUM**

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

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**CLINICAL INSPECTION SUMMARY**

**DATE:** September 12, 2013

**TO:** Jade Pham, Regulatory Health Project Manager  
Linda Hu M.D., Medical Officer  
Vaneeta Tandon, Safety Officer/DNP  
Division of Non-Prescription Clinical Evaluation Products

**FROM:** Antoine El-Hage, Ph.D.  
Good Clinical Practice Assessment Branch  
Division of Good Clinical Practice Compliance  
Office of Scientific Investigations

**THROUGH:** Susan Leibenhaut, M.D.  
Acting Team Leader  
Good Clinical Practice Assessment Branch  
Division of Good Clinical Practice Compliance  
Office of Scientific Investigations

Kassa Ayalew, M.D.  
Acting Branch Chief  
Good Clinical Practice Assessment Branch  
Division of Good Clinical Practice Compliance  
Office of Scientific Investigations

**SUBJECT:** Evaluation of Clinical Inspections

**NDA:** 205-352

**APPLICANT:** Bayer Health Care

**DRUG:** Aleve PM

**NME:** No

**THERAPEUTIC CLASSIFICATION:** Standard review

**INDICATION:** Treatment of occasional sleeplessness associated with minor aches/pain and nighttime sleep aid, and for OTC population

**CONSULTATION REQUEST DATE:** June 21, 2013

**DIVISION ACTION GOAL DATE:** January 17, 2014

**PDUFA DATE:** January 17, 2014

**INSPECTION SUMMARY DUE DATE:** November 20, 2013

## **I. BACKGROUND:**

Bayer Health Care, has submitted this application for the use of Aleve PM in combination with diphenhydramine (DPH) for the relief of occasional sleeplessness associated with minor aches and pain (helps you fall asleep and stay asleep) so that it can be marketed “over the counter” (OTC). Two clinical trials were submitted in support of the application: Impact Trial 14837 (one night/day) in dental extract population and Impact Trial 15560 (10days duration) intended for OTC population when used for 10 consecutive days and was conducted for safety evaluation only. Two protocols were submitted in support of the application.

**Protocols:** Study Impact number 14837 entitled “A Multicenter, Randomized, Double-Blind, Parallel-Group Trial Assessing the Efficacy and Safety of Naproxen Sodium and Diphenhydramine Combination in Postsurgical Dental Pain with Phase Advanced Sleep ”and

Study Impact number 15560 entitled “A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Safety and Tolerability Trial of Naproxen Sodium/Diphenhydramine Combination in an OTC Population” .

### **Investigational Drug**

Bayer HealthCare has developed a novel combination of naproxen sodium and diphenhydramine HCL for consumers who suffer from occasional sleeplessness associated with minor aches and pains and desire enhanced sleep with the convenience of a combination product.

Naproxen has been marketed in prescription form since 1976 under the brand name Naproxen®. In 1994, the FDA approved naproxen sodium tablets, 220mg for over-the-counter (OTC) marketing under the brand name Aleve. Aleve is indicated for the temporary relief of minor aches and pains due to minor pain of arthritis, muscular aches, backaches, headache, toothaches, and the common colds. Aleve should not be taken longer than 10 days for a pain of 3 days for fever unless otherwise directed by a medical doctor.

Diphenhydramine (DPH) is an OTC antihistamine and a nighttime sleep-aid. As a nonprescription nighttime sleep-aid, DHP at a dose of 50mg has been demonstrated with sufficient clinical evidence to be generally safe and effective as one of the main ingredients in approved marketed OTC analgesic/nighttime sleep aid combination products.

Actigraphy is an objective method of recording sleep and wake using a wrist motion monitor. It is a noninvasive tool that measures an individual’s movement from which quantity and timing of sleep are derived. The actigraphy data have been shown to have a positive correlation with polysomnographic scoring. Actigraphy was used to obtain data in discriminating between sleep and wake states in the subjects.

Although Aleve is not an NME, it is currently being reviewed as part of an application for a combination tablet of naproxen sodium 440mg plus diphenhydramine hydrochloride 50 mg which resulted in a sustained relief of pain and impacted on sleep maintenance parameters,

including wake after sleep onset (WASO), total sleep time and sleep efficiency. The applicant is seeking to market Aleve PM as a new combination product. Safety and efficacy in support of the application were based primarily on one day data from Impact 14837 study.

The Applicant-sponsored two studies were submitted in support of the application. This is a brief summary of the studies:

### **Protocol Impact 147837**

The study was a multicenter, randomized, double-blind, parallel group, pivotal efficacy trial. The study consisted of a Screening Visit, a Dosing period and an End of Trial Assessment. Subjects who have undergone surgical extraction of impacted third molar were housed and observed at the Clinical Research Unit overnight and required to go to bed approximately **5 hours** earlier than usual. The single dose administration during the dosing period was evaluated for efficacy. Qualified subjects were administered one of the following 4 treatment groups;

- Naproxen sodium 440mg/DPH 50mg combination treatment group
- Naproxen sodium 220mg/DPH 50mg combination treatment group
- Naproxen sodium 440 mg treatment group: two Aleve (naproxen sodium 220mg tablets)
- DPH 50mg treatment group: two Benadryl® (DPH 25mg tablets)

The objective of this study was to evaluate the efficacy and safety of a single oral dose of two dose combination of naproxen sodium and DPH to demonstrate that naproxen sodium/DPH combination provides added clinical benefit to sleep improvement than either single ingredient alone in subjects with post-surgical dental pain and phase advanced sleep. This study was a one night/day study duration of 10 hours of sleep.

### **Protocol Impact 15560**

The study was a multicenter, randomized, double-blind, placebo-controlled, parallel-group safety and tolerability trial. The trial consisted of a Screening Visit, a Treatment Period, and End of Trial (EOT) Visit. Subjects 12 years and older with a history of occasional sleeplessness associated with minor aches and pains were eligible to participate in the trial. Qualified subjects were randomized to naproxen sodium 440 mg/DHP 50mg or placebo were instructed to take the assigned investigational product (two capsules) with a full glass of water every evening, approximately 30 minutes before bedtime for 10 consecutive days in an outpatient setting. A self-reported daily diary (paper) was provided for subjects to record each dose of the investigational product taken, adverse events that have occurred during the 10-day treatment period, and any concomitant medication taken if any.

Qualified subjects were administered one of the following 2 treatment groups;

- Naproxen sodium 440 mg treatment group: two Aleve ( 2 capsules each naproxen sodium 220mg/DHP 25mg )
- Placebo (2 placebo capsules)

The objective of this study was to evaluate the safety and tolerability of naproxen sodium 440mg/ DPH 50mg compared placebo when used for 10 consecutive days in a population representative of OTC users of analgesic/nighttime sleep-aid combination products. This study was of 10 days duration.

## II. RESULTS (by protocol/site):

Name of CI, location, and Site #	Protocol and # of subjects randomized	Inspection Dates	Final Classification
William Buchanan, M.D 7551 Metro Center Drive Suite 200 Austin, TX 78744 Site #1401	Protocol Impact 14837 Number of subjects: 350	August 5-9, 2013	Pending (preliminary classification NAI)
Lynn Webster, M.D. Life Tree Clinical Research 3838 South 700 East Suite 202 Salt Lake City, UT 84106 Site# 14017	Protocol Impact 15560 Number of subjects: 22	August 19- 22, 2013	Pending (preliminary classification VAI)

### Key to Classifications

NAI = No deviations

VAI = Deviation(s) from regulations

OAI = Significant deviations from regulations. Data unreliable.

Pending = Preliminary classification based on e-mail communication from the field; the Establishment Inspectional Report (EIR) has not been received from the field and complete review of EIR is pending. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIRs.

### 1. William Buchanan, M.D. Austin, TX 78744

- a. What Was Inspected:** This inspection was performed as a data audit for NDA 205-352, Study Protocol Impact 14837. At this site, a total of 578 subjects were screened, 228 subjects were reported as screen failures, 350 subjects were randomized into the study, and 350 subjects completed the study. Review of the Informed Consent Documents, for all subjects reviewed, verified that subjects signed informed consent forms prior to enrollment.

The medical records/source data for 106 subjects were reviewed and compared to data listings. The review included consent forms, drug accountability records, inclusion/exclusion criteria, vital signs, IRB records, sponsor correspondence, and adverse events. Source documents for all subjects were compared to case report forms and data listings including for primary efficacy endpoints and adverse events listings.

- b. General Observations/Commentary:** At the conclusion of the inspection, no Form FDA 483 was issued to Dr. Buchman. The medical records reviewed were found to be in order, organized, and the data verifiable. There were no deaths and no evidence of under-reporting of adverse events. The study appears to have been conducted adequately, and the data generated may be used to support the pending application.
- c. Assessment of Data Integrity:** The data generated in support of the clinical efficacy and safety at Dr. Buchman’s site are considered reliable and acceptable in support of the pending application.

**2. Lynn Webster, M.D.  
Salt Lake City, UT 84106**

- a. What Was Inspected:** This inspection was performed as a data audit for NDA 205-352, Study Protocol Impact 15560. At this site, a total of 25 subjects were screened, three subjects were reported as screen failures, 22 subjects were randomized into the study and 20 subjects completed the study. Review of the Informed Consent Documents, for all subjects records reviewed, verified that all subjects signed informed consent forms prior to enrollment.

The medical records/source documents for 25 subjects (including the 3 screen failures) were reviewed for primary/secondary endpoints. The medical records/source documents for all subjects for certain visits were reviewed including drug accountability records, vital signs, IRB files, inclusion/exclusion criteria, prior and concomitant medications, and adverse events reporting. The field investigator compared the source documents/endpoint values to the data listings for primary efficacy endpoints, and no discrepancies were noted.

- b. General Observations/Commentary:** At the conclusion of the inspection, no Form FDA 483 was issued to Dr. Webster. However, our field investigator noted minor protocol deviations which were discussed with the clinical investigator. The discussion included: Subject 1101 was taking ibuprofen for “pain” one month prior to the study. It is not clear from the source documents whether the subject was taking ibuprofen daily (as defined by 5-7 times a week); Subject 1017 reported not taking the study medication on study day 5, however drug accountability records indicate that the study drug was taken with 100% compliance; Subject 1021 took 35/100 mg acetaminophen tablets throughout the 10 day trial, however, the rescue medication log indicates the subject took more than 1000 mg (2 capsules). The use of OTC medication such as acetaminophen is contraindicated according to the protocol. With the exception of the items noted above, the medical records reviewed were found to be in order and the data verifiable. There were no deaths and no evidence of under-reporting of adverse events. There were no known limitations to the inspection.
- c. Assessment of Data Integrity:** Although minor protocol deviations were noted, the data in support of the clinical efficacy and safety at Dr. Webster’s site are considered reliable and may be used in support of the pending application.

### III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

Two clinical investigator sites were inspected in support of this application. The inspection of the two clinical investigators listed above revealed minor regulatory violations at Dr. Webster's site. The pending classification for Dr. Webster's site is Voluntary Action Indicated (VAI) and the pending classification for Dr. Buchanan inspection is no action indicated (NAI). An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIRs. Overall, the data submitted from these two sites are considered acceptable in support of the pending application.

*{See appended electronic signature page}*

Antoine El-Hage, Ph.D.  
Good Clinical Practice Assessment Branch  
Division of Good Clinical Practice Compliance  
Office of Scientific Investigations

CONCURRENCE:

*{See appended electronic signature page}*

Susan Leibenhaut, M.D.  
Acting Team Leader  
Good Clinical Practice Assessment Branch  
Division of Good Clinical Practice Compliance  
Office of Scientific Investigations

*{See appended electronic signature page}*

Kassa Ayalew, M.D.  
Acting Branch Chief  
Good Clinical Practice Assessment Branch  
Division of Good Clinical Practice Compliance  
Office of Scientific Investigations

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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ANTOINE N EL HAGE  
09/13/2013

SUSAN LEIBENHAUT  
09/13/2013

KASSA AYALEW  
09/13/2013



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/s/  
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BARBARA R COHEN  
06/30/2013

LESLEYANNE FURLONG  
07/01/2013

## RPM FILING REVIEW

(Including Memo of Filing Meeting)

**To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]**

Application Information		
NDA # 205352 BLA#	NDA Supplement #:S- BLA Supplement #	Efficacy Supplement Type SE-
Proprietary Name: Aleve PM Established/Proper Name: naproxen sodium, 220 mg / diphenhydramine hydrochloride, 25 mg Dosage Form: tablets Strengths: 220 mg and 25 mg		
Applicant: Bayer Healthcare, LLC - Consumer care Agent for Applicant (if applicable): N/A		
Date of Application: 03/20/13 Date of Receipt: 03/20/13 Date clock started after UN: N/A		
PDUFA Goal Date: 01/20/14	Action Goal Date (if different): 01/17/14	
Filing Date: 05/19/13	Date of Filing Meeting: 05/09/13	
Chemical Classification: (1,2,3 etc.) (original NDAs only) Type 4		
Proposed indication(s)/Proposed change(s): nighttime pn relief		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
<b><i>If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:  <a href="http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499">http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499</a>                      and refer to Appendix A for further information.</i></b>		
Review Classification:  <b><i>If the application includes a complete response to pediatric WR, review classification is Priority.</i></b>  <b><i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i></b>	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority  <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted	
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>	
Part 3 Combination Product? <input type="checkbox"/>  <b><i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i></b>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)	

<input type="checkbox"/> Fast Track Designation <input type="checkbox"/> Breakthrough Therapy Designation <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation  <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input checked="" type="checkbox"/> Direct-to-OTC	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Other:				
Collaborative Review Division ( <i>if OTC product</i> ): DNP				
List referenced IND Number(s): 103407				
<b>Goal Dates/Product Names/Classification Properties</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
PDUFA and Action Goal dates correct in tracking system?  <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	X			
Are the proprietary, established/proper, and applicant names correct in tracking system?  <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	X			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at: <a href="http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm">http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm</a></i>  <i>If no, ask the document room staff to make the appropriate entries.</i>	X			
<b>Application Integrity Policy</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a></i>		X		
<b>If yes, explain in comment column.</b>			X	
<b>If affected by AIP, has OC/OMPQ been notified of the submission? If yes, date notified: N/A</b>			X	
<b>User Fees</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			

<p><u>User Fee Status</u></p> <p><i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i></p>	<p>Payment for this application:</p> <p><input checked="" type="checkbox"/> Paid  <input type="checkbox"/> Exempt (orphan, government)  <input type="checkbox"/> Waived (e.g., small business, public health)  <input type="checkbox"/> Not required</p>																			
<p><i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i></p>	<p>Payment of other user fees:</p> <p><input checked="" type="checkbox"/> Not in arrears  <input type="checkbox"/> In arrears</p>																			
<p><b>505(b)(2) (NDAs/NDA Efficacy Supplements only)</b></p>	<p><b>YES</b></p>	<p><b>NO</b></p>	<p><b>NA</b></p>	<p><b>Comment</b></p>																
<p>Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p>			<p>X</p>																	
<p>Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].</p>			<p>X</p>																	
<p>Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?</p> <p><i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs</i></p>			<p>X</p>																	
<p>Is there unexpired exclusivity on any drug product containing the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)?</p> <p><i>Check the Electronic Orange Book at:</i>  <a href="http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm">http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</a></p> <p><b>If yes, please list below:</b></p> <table border="1" data-bbox="203 1482 1349 1619"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration															<p>X</p>	
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.</i></p>																				
<p><b>Exclusivity</b></p>	<p><b>YES</b></p>	<p><b>NO</b></p>	<p><b>NA</b></p>	<p><b>Comment</b></p>																
<p>Does another product (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug</i></p>		<p>X</p>																		

<b>Designations and Approvals list at:</b> <a href="http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm">http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm</a>				
<b>If another product has orphan exclusivity</b> , is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?  <i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>			X	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (NDAs/NDA efficacy supplements only)  If yes, # years requested: 3  <i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	X			
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (NDAs only)?		X		
<b>If yes</b> , did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?  <i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i>			X	

Format and Content				
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic)  <input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?	N/A			
<b>Overall Format/Content</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
If electronic submission, does it follow the eCTD guidance? <sup>1</sup> If not, explain (e.g., waiver granted).	X			
<b>Index:</b> Does the submission contain an accurate comprehensive index?	X			
Is the submission complete as required under 21 CFR 314.50 (NDAs/NDA efficacy supplements) or under 21 CFR 601.2 (BLAs/BLA efficacy supplements) including:	X			

1

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

<input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)				
<b>If no, explain.</b>				
<b>BLAs only:</b> Companion application received if a shared or divided manufacturing arrangement?			<b>X</b>	
<b>If yes, BLA #</b>				
<b>Forms and Certifications</b>				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, <b>paper</b> forms and certifications with hand-written signatures must be included. <b>Forms</b> include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); <b>Certifications</b> include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
<b>Application Form</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	X			
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	X			
<b>Patent Information (NDAs/NDA efficacy supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	X			
<b>Financial Disclosure</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	X			
<i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
<b>Clinical Trials Database</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is form FDA 3674 included with authorized signature?	X			
<i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i>				

<i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>				
<b>Debarment Certification</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p>Is a correctly worded Debarment Certification included with authorized signature?</p> <p><i>Certification is not required for supplements if submitted in the original application; If foreign applicant, <b>both</b> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i></p> <p><i>Note: Debarment Certification should use wording in FD&amp;C Act Section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</i></p>	X			
<b>Field Copy Certification (NDAs/NDA efficacy supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p><b>For paper submissions only:</b> Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>			X	
<b>Controlled Substance/Product with Abuse Potential</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p><u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</p> <p><i>If yes, date consult sent to the Controlled Substance Staff:</i></p> <p><u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i></p>			X	

<b>Pediatrics</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p><b><u>PREA</u></b></p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC RPM (PeRC meeting is required)<sup>2</sup></i></p> <p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver &amp; deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p>	X			PeRC scheduled for 10/2/13
<p><b>If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?</b></p>		X		
<p><b>If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included?</b></p> <p><i>If no, request in 74-day letter</i></p>	X			
<p><b>If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)?</b></p> <p><i>If no, request in 74-day letter</i></p>		X		
<p><b><u>BPCA</u> (NDAs/NDA efficacy supplements only):</b></p> <p>Is this submission a complete response to a pediatric Written Request?</p> <p><i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)<sup>3</sup></i></p>		X		
<b><u>Proprietary Name</u></b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p>Is a proposed proprietary name submitted?</p> <p><i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i></p>	X			
<b><u>REMS</u></b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p>Is a REMS submitted?</p> <p><i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i></p>		X		
<b><u>Prescription Labeling</u></b>	<input checked="" type="checkbox"/> <b>Not applicable</b>			
Check all types of labeling submitted.	<input type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide)			

<sup>2</sup> <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

<sup>3</sup> <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

	<input type="checkbox"/> Carton labels <input type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is Electronic Content of Labeling (COL) submitted in SPL format?  <i>If no, request applicant to submit SPL before the filing date.</i>			X	
Is the PI submitted in PLR format? <sup>4</sup>			X	
<b>If PI not submitted in PLR format</b> , was a waiver or deferral requested before the application was received or in the submission? <b>If requested before application was submitted</b> , what is the status of the request?  <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>			X	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?			X	
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)			X	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?			X	
<b>OTC Labeling</b>	<input type="checkbox"/> <b>Not Applicable</b>			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Outer carton label <input checked="" type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input checked="" type="checkbox"/> Other (specify) <b>Consumer Pouch</b>			
	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is electronic content of labeling (COL) submitted?  <i>If no, request in 74-day letter.</i>	X			
Are annotated specifications submitted for all stock keeping units (SKUs)?  <i>If no, request in 74-day letter.</i>		X		Bayer will need to submit outer carton labels for the 2-count pouches or describe how they will be displayed and sold. Bayer will need to submit a list of all

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

				SKUs to be sold under this NDA and labels for any SKUs which were not submitted.
If representative labeling is submitted, are all represented SKUs defined?  <i>If no, request in 74-day letter.</i>			X	
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?			X	
<b>Other Consults</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)  <i>If yes, specify consult(s) and date(s) sent:</i>	X			1. DAAAP 5/7/13 2. OSI Consult for BIMO to be sent.
<b>Meeting Minutes/SPAs</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
End-of Phase 2 meeting(s)? <b>Date(s):</b>  <i>If yes, distribute minutes before filing meeting</i>		X		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? <b>Date(s):</b> 10/09/12  <i>If yes, distribute minutes before filing meeting</i>	X			
Any Special Protocol Assessments (SPAs)? <b>Date(s):</b> 09/07/10  <i>If yes, distribute letter and/or relevant minutes before filing meeting</i>	X			

ATTACHMENT

**MEMO OF FILING MEETING**

**DATE:** 05/09/13

**BLA/NDA/Supp #:** NDA 205352

**PROPRIETARY NAME:** Aleve PM

**ESTABLISHED/PROPER NAME:** naproxen Na/DPH

**DOSAGE FORM/STRENGTH:** 220 mg / 25 mg

**APPLICANT:** Bayer Healthcare, LLC – Consumer Care

**PROPOSED INDICATION(S)/PROPOSED CHANGE(S):** nighttime pain relief

**BACKGROUND:**

**REVIEW TEAM:**

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Jeffrey Buchanan	Y
	CPMS/TL:	Dan Brum	Y
Cross-Discipline Team Leader (CDTL)	Lesley Furlong		Y
Clinical	Reviewer:	Linda Hu	Y
	TL:	Lesley Furlong	Y
Social Scientist Review ( <i>for OTC products</i> )	Reviewer:		
	TL:		
OTC Labeling Review ( <i>for OTC products</i> )	Reviewer:	Kate Phelan	Y
	TL:	Steve Adah	Y
Clinical Microbiology ( <i>for antimicrobial products</i> )	Reviewer:		
	TL:		

Clinical Pharmacology	Reviewer:	Xinning Yang	Y
	TL:	Angela Men	Y
Biostatistics	Reviewer:	Julia Luan	Y
	TL:	Kun Jin	N
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Cindy Li	Y
	TL:		
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) ( <i>for BLAs/BLA efficacy supplements</i> )	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Swapan De	Y
	TL:	Danae Christodoulou	N
Quality Microbiology ( <i>for sterile products</i> )	Reviewer:		
	TL:		
CMC Labeling Review	Reviewer:	Swapan De	Y
	TL:	Danae Chistodoulou	N
Facility Review/Inspection	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:	Alice Tu	Y
	TL:	Todd Bridges	Y
OSE/DRISK (REMS)	Reviewer:		
	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:	Sharon Gershon	Y
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
BioPharm	Reviewer: Minerva Hughes		Y
	TL: John Duan		Y
DPARP	Reviewer: Liz Kilgore		Y
	TL: Ellen Fields		Y
DNP	Reviewer: Veneeta Tandon		Y
	TL: Ron Farkas		Y

**FILING MEETING DISCUSSION:**

<p><b>GENERAL</b></p> <ul style="list-style-type: none"> <li>• 505(b)(2) filing issues: <ul style="list-style-type: none"> <li>○ Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</li> <li>○ Did the applicant provide a scientific “bridge” demonstrating the relationship between the proposed product and the referenced product(s)/published literature?</li> </ul> </li> </ul> <p>Describe the scientific bridge (e.g., BA/BE studies):</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>• Per reviewers, are all parts in English or English translation?</li> </ul> <p><b>If no, explain:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>• Electronic Submission comments</li> </ul> <p><b>List comments:</b> none</p>	<input type="checkbox"/> Not Applicable
<p><b>CLINICAL</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>• Clinical study site(s) inspections(s) needed?</li> </ul>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<b>If no, explain:</b>	
<ul style="list-style-type: none"> <li>• Advisory Committee Meeting needed?</li> </ul> <p><b>Comments:</b></p> <p><i>If no, for an NME NDA or original BLA , include the reason. For example:</i></p> <ul style="list-style-type: none"> <li>○ <i>this drug/biologic is not the first in its class</i></li> <li>○ <i>the clinical study design was acceptable</i></li> <li>○ <i>the application did not raise significant safety or efficacy issues</i></li> <li>○ <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i></li> </ul>	<input type="checkbox"/> YES Date if known: N/A <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined  Reason:
<ul style="list-style-type: none"> <li>• Abuse Liability/Potential</li> </ul> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?</li> </ul> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b>CLINICAL MICROBIOLOGY</b></p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<p><b>CLINICAL PHARMACOLOGY</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>• Clinical pharmacology study site(s) inspections(s) needed?</li> </ul>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<p><b>BIostatISTICS</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE

<b>Comments:</b>	<input type="checkbox"/> Review issues for 74-day letter
<b>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</b>  <b>Comments:</b>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input checked="" type="checkbox"/> Review issues for 74-day letter
<b>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</b>  <b>Comments:</b>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<b>PRODUCT QUALITY (CMC)</b>  <b>Comments:</b>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<u><b>Environmental Assessment</b></u>  <ul style="list-style-type: none"> <li>• Categorical exclusion for environmental assessment (EA) requested?   <b>If no</b>, was a complete EA submitted?</li> <li><b>If EA submitted</b>, consulted to EA officer (OPS)?</li> </ul> <b>Comments:</b>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO  <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO  <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<u><b>Quality Microbiology (for sterile products)</b></u>  <ul style="list-style-type: none"> <li>• Was the Microbiology Team consulted for validation of sterilization? (<b>NDAs/NDA supplements only</b>)</li> </ul> <b>Comments:</b>	<input checked="" type="checkbox"/> Not Applicable  <input type="checkbox"/> YES <input type="checkbox"/> NO

<p><b><u>Facility Inspection</u></b></p> <ul style="list-style-type: none"> <li>• Establishment(s) ready for inspection?</li> <li>▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ?</li> </ul> <p><b>Comments:</b></p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><b><u>Facility/Microbiology Review (BLAs only)</u></b></p> <p><b>Comments:</b></p>	<p><input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><b><u>CMC Labeling Review</u></b></p> <p><b>Comments:</b></p>	<p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><b>APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)</b></p> <ul style="list-style-type: none"> <li>• Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application?</li> <li>• If so, were the late submission components all submitted within 30 days?</li> </ul>	<p><input checked="" type="checkbox"/> N/A</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<ul style="list-style-type: none"> <li>• What late submission components, if any, arrived after 30 days?</li> </ul>	<p>Information request was sent to the applicant requiring submission of the validation reports for the bioassays used to analyze PK samples from Study 16135, and submission of datasets in xpt format for raw PK data and PK parameters. The applicant submitted the required documents on May 15, 2013.</p>

<ul style="list-style-type: none"> <li>Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?</li> </ul>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Is a comprehensive and readily located list of all clinical sites included or referenced in the application?</li> </ul>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?</li> </ul>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<b>REGULATORY PROJECT MANAGEMENT</b>	
<p><b>Signatory Authority:</b> Shaw Chen, MD, PhD</p> <p><b>Date of Mid-Cycle Meeting</b> (for NME NDAs/BLAs in “the Program” PDUFA V):</p> <p><b>21<sup>st</sup> Century Review Milestones (see attached)</b> (listing review milestones in this document is optional):</p> <p><b>Comments:</b></p>	
<b>REGULATORY CONCLUSIONS/DEFICIENCIES</b>	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	The application, on its face, appears to be suitable for filing.  <u>Review Issues:</u>  <input type="checkbox"/> No review issues have been identified for the 74-day letter.  <input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional):  <u>Review Classification:</u>  <input checked="" type="checkbox"/> Standard Review  <input type="checkbox"/> Priority Review
<b>ACTIONS ITEMS</b>	
<input type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product

	Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input type="checkbox"/>	If priority review: <ul style="list-style-type: none"> <li>• notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices)</li> <li>• notify OMPQ (so facility inspections can be scheduled earlier)</li> </ul>
<input type="checkbox"/>	Send review issues/no review issues by day 74
<input type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	Update the PDUFA V DARRTS page (for NME NDAs in the Program)
<input type="checkbox"/>	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found in the CST eRoom at: <a href="http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f">http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f</a> ]
<input type="checkbox"/>	Other

## Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),
- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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JEFFREY A BUCHANAN  
05/31/2013

# Filing Review for Aleve PM

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**SUBMISSION DATES:** March 20, 2013

**NDA/SUBMISSION TYPE:** 205-352 (original NDA)

**ACTIVE INGREDIENTS:** 220 mg naproxen sodium and 25 mg diphenhydramine hydrochloride

**DOSAGE FORMS:** tablet

**SPONSOR:** Bayer HealthCare  
Leonard M. Baum, R.Ph.,  
Vice President, Regulatory Affairs – North America  
(973) 254-4672

**REVIEWER:** Kathleen M. Phelan, R.Ph.

**TEAM LEADER:** Steven Adah, PhD

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<b>Submitted Labeling</b>	<b>Representative of Following SKUs</b>
2-count pouch, front and back	none
20-, 40-, and 80-count immediate container, front and back	none
20-, 40-, and 80-count outer carton	none

Issues	Yes/No	Comments
Is the supplement correctly assigned as a PA, CBE0, CBE30?	N/A	This is an original NDA.
Are the outer container and immediate container labels, and consumer information leaflet and other labeling included for all submitted SKUs?	No	Sponsor should submit the outer carton for the 2-count pouch or explain how the pouch will be displayed without an outer carton.
If representative labeling is submitted, does the submitted labeling represent only SKUs of different count sizes (same flavor and dosage form)?	N/A	The submission does not state that any submitted labels represent other labels.
Is distributor labeling included?	No	
Does the submission include the annotated specifications for the Drug Facts label?	Yes	
Is Drug Facts title and Active ingredient/Purpose section of Drug Facts label visible at time of purchase?	No	Sponsor should clarify how the 2-count pouch will be displayed.
Do any of the labels include "prescription strength" or similar statements?	No	
Do any of the labels include "#1 doctor recommended" or similar endorsement statements?	No	
Do any labels include text in a language other than English?	No	
Is a new trade name being proposed? If multiple trade names, is the primary or preferred trade name identified?	Yes	The sponsor requested a trade-name review.
Does a medical officer need to review any clinical issues?	Yes	This is an original NDA requiring review by a medical officer.
If SLR, should ONDQA also review?	Yes	This is an original NDA requiring ONDQA review.

### Information Request:

Information request is necessary. Please request the following:

- an outer carton label for the 2-count pouch SKU or, if there is no outer carton, a description of how the pouches will be displayed and sold
- a list of all SKUs to be sold under this NDA and labels for any SKUs that were not submitted.

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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KATHLEEN M PHELAN  
05/08/2013

STEVEN A ADAH  
05/08/2013