

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

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PROPRIETARY NAME REVIEW(S)

**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**

Proprietary Name Review

Date: June 21, 2013

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Drug Name and Strength: Aleve PM

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Applicant/Sponsor: Bayer

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CONTENTS

1	INTRODUCTION.....	1
1.1	Regulatory History	1
1.2	Product Information.....	2
2	RESULTS.....	3
2.1	Promotional Assessment	3
2.2	Safety Assessment.....	3
3	CONCLUSIONS	6
3.1	Comments to the Applicant.....	6
4	REFERENCES	7
	APPENDICES.....	10

1 INTRODUCTION

This review evaluates the proposed proprietary name, Aleve PM, from a safety and promotional perspective. The sources and methods used to evaluate the proposed name are outlined in the reference section and Appendix A, respectively.

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. 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 is currently also seeking approval for (b) (4)

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

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)	(b) (4)			
Aleve PM*** [Proposed]	Tablets	Naproxen sodium/ Diphenhydramine HCl	200 mg/ 25 mg	NDA 205352
(b) (4)				

1.2 PRODUCT INFORMATION

The following product information is provided in the March 28, 2013 proprietary name submission. The intended pronunciation is A-lēve/'pē/'em.

Drug Facts	
Active Ingredients	Purposes (in each caplet)
Diphenhydramine hydrochloride 25 mg.....Nighttime sleep-aid	
Naproxen sodium 220 mg (naproxen 200 mg) (NSAID)*.....Pain reliever	
*nonsteroidal anti-inflammatory drug	
Uses	
<ul style="list-style-type: none"> for relief of occasional sleeplessness when associated with minor aches and pains helps you fall asleep and stay asleep 	
Warnings	
<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"> hives facial swelling asthma (wheezing) shock skin reddening rash blisters <p>If an allergic reaction occurs, stop use and seek medical help right away.</p> <p>Stomach bleeding warning: This product contains an NSAID, which may cause severe stomach bleeding. The chance is higher if you:</p> <ul style="list-style-type: none"> are age 60 or older have had stomach ulcers or bleeding problems take a blood thinning (anticoagulant) or steroid drug take other drugs containing prescription or nonprescription NSAIDs (aspirin, ibuprofen, naproxen, or others) have 3 or more alcoholic drinks every day while using this product take more or for a longer time than directed 	
Do not use	
<ul style="list-style-type: none"> if you have ever had an allergic reaction to any other pain reliever/fever reducer unless you have time for a full night's sleep in children under 12 years of age 	

Drug Facts (continued)
<ul style="list-style-type: none"> right before or after heart surgery with any other product containing diphenhydramine, even one used on skin if you have sleeplessness without pain <p>Ask a doctor before use if</p> <ul style="list-style-type: none"> stomach bleeding warning applies to you you have problems or serious side effects from taking pain relievers or fever reducers you have a history of stomach problems, such as heartburn you have high blood pressure, heart disease, liver cirrhosis, kidney disease, or asthma you are taking a diuretic you have a breathing problem such as emphysema or chronic bronchitis you have glaucoma you have trouble urinating due to an enlarged prostate gland <p>Ask a doctor or pharmacist before use if you are</p> <ul style="list-style-type: none"> taking sedatives or tranquilizers, or any other sleep-aid under a doctor's care for any serious condition taking any other antihistamines taking any other drug <p>When using this product</p> <ul style="list-style-type: none"> drowsiness will occur avoid alcoholic drinks do not drive a motor vehicle or operate machinery take with food or milk if stomach upset occurs the risk of heart attack or stroke may increase if you use more than directed or for longer than directed <p>Stop use and ask a doctor if</p> <ul style="list-style-type: none"> you experience any of the following signs of stomach bleeding: <ul style="list-style-type: none"> feel faint vomit blood have bloody or black stools have stomach pain that does not get better pain gets worse or lasts more than 10 days sleeplessness persists continuously for more than 2 weeks. Insomnia may be a symptom of a serious underlying medical illness. redness or swelling is present in the painful area any new symptoms appear you have difficulty swallowing it feels like the pill is stuck in your throat <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>

Drug Facts (continued)
Directions
<ul style="list-style-type: none"> do not take more than directed drink a full glass of water with each dose adults and children 12 years and over: take 2 caplets at bedtime do not take more than 2 caplets in 24 hours if taken with food, this product may take longer to work
Other information
<ul style="list-style-type: none"> read all warnings and directions before use each caplet contains: sodium 20 mg store at 20-25°C (68-77°F) avoid high humidity and excessive heat above 40°C (104°F)
Inactive ingredients
carnauba wax, FD&C blue #2 aluminum lake, hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, povidone, purified water, talc, titanium dioxide
Questions or comments?
1-800-395-0689 (Mon – Fri 9AM – 5PM EST) (b) (4)

Bayer

2 RESULTS

The following sections provide the information obtained and considered in the overall evaluation of the proposed proprietary name.

2.1 PROMOTIONAL ASSESSMENT

DMEPA determined the proposed name is acceptable from a promotional perspective.

2.2 SAFETY ASSESSMENT

The following aspects were considered in the safety evaluation of the name.

2.2.1 *United States Adopted Names (USAN) Search*

The April 8, 2013 search of the United States Adopted Name (USAN) stems did not identify that a USAN stem is present in the proposed proprietary name.

2.2.2 *Components of the Proposed Proprietary Name*

The Applicant indicated in their submission that the proposed name, Aleve PM, is derived from the trademarked proprietary name “Aleve” for Bayer’s Naproxen Sodium products and the modifier “PM” to clearly differentiate this nighttime product from the single-ingredient Naproxen Sodium Tablets. The intended meaning of the modifier “PM” is to convey the product’s intended nighttime use. However, it also represents an additional active ingredient Diphenhydramine. The Applicant further indicated that this naming practice is consistent with other NDA and monograph OTC (over-the-counter) analgesic nighttime sleep-aid products such as Advil PM, Tylenol PM, Excedrin PM, and Motrin PM. The evaluation of this proposed modifier is discussed in Section 2.2.7.

2.2.3 *Medication Error Data Selection of Cases*

DMEPA searched FAERS Adverse Event Reporting System (FAERS) database on April 8, 2013 for medication errors involving name or label confusion with Aleve. The search terms used appear 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. This search strategy did not retrieve any medication error cases relevant to this review.

Table 2: FAERS Search Strategy on April 8, 2013	
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)

2.2.4 FDA Name Stimulation Studies

Fifty-one practitioners participated in DMEPA’s prescription studies. Forty practitioners interpreted the name correctly as “Aleve PM”. One practitioner omitted the modifier “PM” in his/her response, and therefore, the interpretation reflects the currently marketed “Aleve” product. However, the remaining misinterpretations did not overlap with any currently marketed products nor did they appear or sound similar to any currently marketed products or products under development. A common misinterpretation was “Alleve PM” with a double “L” in the base brand name (n=2 in voice study, and n=1 in inpatient written study). DMEPA considered the misinterpretation in their assessment of similar names (See Appendix B). See Appendix C for the complete listing of interpretations from the verbal and written prescription studies.

2.2.5 Comments from Other Review Disciplines

In response to the OSE, March 29, 2013 e-mail, the Division of Nonprescription Clinical Evaluation (DNCE) did not forward any comments or concerns relating to the proposed name at the initial phase of the proprietary name review.

2.2.6 Failure Mode and Effects Analysis of Similar Names

Appendix B also lists additional possible orthographic and phonetic misinterpretations of the letters appearing in the proposed proprietary name, Aleve PM. Table 3 lists the names with potential orthographic, phonetic, or spelling similarity to the proposed proprietary name, Aleve PM, identified by the primary reviewer, the Expert Panel Discussion (EPD), and other review disciplines.

Table 3. Names with potential orthographic, phonetic, or spelling similarity to Aleve PM

Row #	Look Similar					
	Name	Source	Name	Source	Name	Source
1.	Acova	FDA	Alesse	FDA	Altace	FDA
2.	Adoxa	FDA	Alexin	FDA	Aluvea	FDA
3.	Advil PM	FDA	Allegra D	FDA	Ativan	FDA
4.	Alavert	FDA	(b) (4)	FDA	Tofranil PM	FDA
5.	(b) (4)	FDA	Alora	FDA	Uloric	FDA
6.	Alera	FDA	Aloxi	FDA	Verelan PM	FDA
	Look and Sound Similar					
	Name	Source	Name	Source	Name	Source
7.	Aleve	FDA	Aleve-D Sinus & Cold	FDA		
8.	(b) (4)	FDA	(b) (4)	FDA		

Our analysis of the 22 names contained in Table 3 considered the information obtained in the previous sections along with their product characteristics. The majority of these names already co-exist with the Aleve product line and we have no reported confusion (See Appendix D). Therefore, we do not expect the proposed name Aleve PM to

increase the risk of confusion with the majority of these names in Table 3. The products most at risk for confusion with Aleve PM are the Aleve product line.

Aleve PM will be an extension of the Aleve product line (See Table 1 on page 1). Typically, product line confusion occurs when the modifier is omitted. However, this risk already exists within the Aleve product line. We are not aware of any within product line name confusion at this time. Therefore, we do not expect the addition of the proposed name, Aleve PM to exacerbate the risk of name confusion within the Aleve product line.

2.2.7 Evaluation of “PM” Modifier

The Applicant states the intended meaning of the modifier PM is “nighttime use”. According to MediLexicon (<http://www.medilexicon.com/medicalabbreviations.php>, accessed May 1, 2013), the abbreviation PM stands for after noon, postmortem, picometer and an array of medical terms. DMEPA normally discourages the incorporation of common medical abbreviations (e.g., PM) and coined abbreviations in proprietary names. However, the abbreviation “PM” already exists in proprietary names of currently marketed OTC products in the analgesic drug class (See Table 4). In addition, from post-marketing surveillance of OTC products in Table 4, we are not aware any medication error associated with the misinterpretation of the abbreviation “PM”.

Additionally, in each one of these cases the modifier PM appears to reference the product’s intended nighttime use and represents the active ingredient Diphenhydramine (See Table 4 on page 6). In each case the name contained the original active ingredient which is represented by the root name, and the modifier PM represents the added ingredient Diphenhydramine. The use, active ingredient, and nomenclature (root name “Aleve” plus the modifier “PM”) of the proposed product is consistent with existing OTC oral analgesic products utilizing the “PM” modifier in their proprietary names. Furthermore, the abbreviation “PM” is not listed on ISMP’s List of Error-Prone Abbreviations, Symbols, and Dose Designations¹, or on NCC MERP’s list of Dangerous Abbreviations².

Given the standard use of the modifier PM (diphenhydramine and nighttime), we have no reason to object to this modifier at this point in time.

¹ ISMP. ISMP’s List of Error-Prone Abbreviations, Symbols, and Dose Designations. Online at <http://www.ismp.org/Tools/errorproneabbreviations.pdf>. Accessed May 1, 2013.

² NCC MERP. Dangerous Abbreviations. Online at <http://www.nccmerp.org/dangerousAbbrev.html>. Accessed May 1, 2013.

Table 4. “PM” in OTC Nomenclature

Product Name	Active Ingredients	Strengths	Uses
Advil PM	Ibuprofen/ Diphenhydramine HCl, or Ibuprofen/ Diphenhydramine citrate	200 mg/25 mg 200 mg/38 mg	Relief of occasional sleeplessness when associated with minor aches and pains. Helps you fall asleep and stay sleep.
Motrin PM	Ibuprofen/ Diphenhydramine citrate	200 mg/38 mg	
Excedrin PM	Acetaminophen/ Diphenhydramine citrate	500 mg/38 mg	Temporary relief of occasional headaches and minor aches and pains with accompanying sleeplessness.
Tylenol PM	Acetaminophen/ Diphenhydramine HCl	500 mg/25 mg	

3 CONCLUSIONS

The proposed proprietary name, Aleve PM, is acceptable from both a promotional and safety perspective.

If you have questions or need clarifications, please contact Ermias Zerislassie, OSE project manager, at 301-796-0097.

3.1 COMMENTS TO THE APPLICANT

We have completed our review of the proposed proprietary name, Aleve PM, and have concluded that this name is acceptable. However, if any of the proposed product characteristics as stated in your March 28, 2013 submission are altered, the name must be resubmitted for review.

Additionally, the proposed proprietary name must be re-reviewed 90 days prior to approval of the NDA. The conclusions upon re-review are subject to change.

4 REFERENCES

1. ***Micromedex Integrated Index*** (<http://csi.micromedex.com>)

Micromedex contains a variety of databases covering pharmacology, therapeutics, toxicology and diagnostics.

2. ***Phonetic and Orthographic Computer Analysis (POCA)***

POCA is a database which was created for the Division of Medication Error Prevention and Analysis, FDA. As part of the name similarity assessment, proposed names are evaluated via a phonetic/orthographic algorithm. The proposed proprietary name is converted into its phonemic representation before it runs through the phonetic algorithm. Likewise, an orthographic algorithm exists which operates in a similar fashion.

3. ***Drug Facts and Comparisons, online version, St. Louis, MO***
(<http://factsandcomparisons.com>)

Drug Facts and Comparisons is a compendium organized by therapeutic course; it contains monographs on prescription and OTC drugs, with charts comparing similar products. This database also lists the orphan drugs.

4. ***FDA Document Archiving, Reporting & Regulatory Tracking System [DARRTS]***

DARRTS is a government database used to organize Applicant and Sponsor submissions as well as to store and organize assignments, reviews, and communications from the review divisions.

5. ***Division of Medication Errors Prevention and Analysis proprietary name consultation requests***

This is a list of proposed and pending names that is generated by the Division of Medication Error Prevention and Analysis from the Access database/tracking system.

6. ***Drugs@FDA*** (<http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm>)

Drugs@FDA contains most of the drug products approved since 1939. The majority of labels, approval letters, reviews, and other information are available for drug products approved from 1998 to the present. Drugs@FDA contains official information about FDA approved brand name, generic drugs, therapeutic biological products, prescription and over-the-counter human drugs and discontinued drugs and “Chemical Type 6” approvals.

7. ***U.S. Patent and Trademark Office*** (<http://www.uspto.gov>)

USPTO provides information regarding patent and trademarks.

8. ***Clinical Pharmacology Online*** (www.clinicalpharmacology-ip.com)

Clinical Pharmacology contains full monographs for the most common drugs in clinical use, plus mini monographs covering investigational, less common,

combination, nutraceutical and nutritional products. It also provides a keyword search engine.

9. *Data provided by Thomson & Thomson's SAEGIS™ Online Service, available at (www.thomson-thomson.com)*

The Pharma In-Use Search database contains over 400,000 unique pharmaceutical trademarks and trade names that are used in about 50 countries worldwide. The data is provided under license by IMS HEALTH.

10. *Natural Medicines Comprehensive Databases (www.naturaldatabase.com)*

Natural Medicines contains up-to-date clinical data on the natural medicines, herbal medicines, and dietary supplements used in the western world.

11. *Access Medicine (www.accessmedicine.com)*

Access Medicine® from McGraw-Hill contains full-text information from approximately 60 titles; it includes tables and references. Among the titles are: Harrison's Principles of Internal Medicine, Basic & Clinical Pharmacology, and Goodman and Gilman's The Pharmacologic Basis of Therapeutics.

12. *USAN Stems (<http://www.ama-assn.org/ama/pub/about-ama/our-people/coalitions-consortiums/united-states-adopted-names-council/naming-guidelines/approved-stems.shtml>)*

USAN Stems List contains all the recognized USAN stems.

13. *Red Book (www.thomsonhc.com/home/dispatch)*

Red Book contains prices and product information for prescription, over-the-counter drugs, medical devices, and accessories.

14. *Lexi-Comp (www.lexi.com)*

Lexi-Comp is a web-based searchable version of the Drug Information Handbook.

15. *Medical Abbreviations (www.medilexicon.com)*

Medical Abbreviations dictionary contains commonly used medical abbreviations and their definitions.

16. *CVS/Pharmacy (www.CVS.com)*

This database contains commonly used over the counter products not usually identified in other databases.

17. *Walgreens (www.walgreens.com)*

This database contains commonly used over the counter products not usually identified in other databases.

18. Rx List (www.rxlist.com)

RxList is an online medical resource dedicated to offering detailed and current pharmaceutical information on brand and generic drugs.

19. Dogpile (www.dogpile.com)

Dogpile is a [Metasearch](#) engine that searches multiple search engines including Google, Yahoo! and Bing, and returns the most relevant results to the search.

20. Natural Standard (<http://www.naturalstandard.com>)

Natural Standard is a resource that aggregates and synthesizes data on complementary and alternative medicine.

APPENDICES

Appendix A

FDA's Proprietary Name Risk Assessment considers the promotional and safety aspects of a proposed proprietary name. The promotional review of the proposed name is conducted by OPDP. OPDP evaluates proposed proprietary names to determine if they are overly fanciful, so as to misleadingly imply unique effectiveness or composition, as well as to assess whether they contribute to overstatement of product efficacy, minimization of risk, broadening of product indications, or making of unsubstantiated superiority claims. OPDP provides their opinion to DMEPA for consideration in the overall acceptability of the proposed proprietary name.

The safety assessment is conducted by DMEPA. DMEPA staff search a standard set of databases and information sources to identify names that are similar in pronunciation, spelling, and orthographically similar when scripted to the proposed proprietary name. Additionally, we consider inclusion of USAN stems or other characteristics that when incorporated into a proprietary name may cause or contribute to medication errors (i.e., dosing interval, dosage form/route of administration, medical or product name abbreviations, names that include or suggest the composition of the drug product, etc.). DMEPA defines a medication error as any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer.³

Following the preliminary screening of the proposed proprietary name, DMEPA gathers to discuss their professional opinions on the safety of the proposed proprietary name. This meeting is commonly referred to the Center for Drug Evaluation and Research (CDER) Expert Panel discussion. DMEPA also considers other aspects of the name that may be misleading from a safety perspective. DMEPA staff conducts a prescription simulation studies using FDA health care professionals. When provided, DMEPA considers external proprietary name studies conducted by or for the Applicant/Sponsor and incorporates the findings of these studies into the overall risk assessment.

The DMEPA primary reviewer assigned to evaluate the proposed proprietary name is responsible for considering the collective findings, and provides an overall risk assessment of the proposed proprietary name. DMEPA bases the overall risk assessment on the findings of a Failure Mode and Effects Analysis (FMEA) of the proprietary name and misleading nature of the proposed proprietary name with a focus on the avoidance of medication errors.

DMEPA uses the clinical expertise of its staff to anticipate the conditions of the clinical setting where the product is likely to be used based on the characteristics of the proposed product. DMEPA considers the product characteristics associated with the proposed product throughout the risk assessment because the product characteristics of the

³ National Coordinating Council for Medication Error Reporting and Prevention.
<http://www.nccmerp.org/about/MedErrors.html>. Last accessed 10/11/2007.

proposed may provide a context for communication of the drug name and ultimately determine the use of the product in the *usual* clinical practice setting.

Typical product characteristics considered when identifying drug names that could potentially be confused with the proposed proprietary name include, but are not limited to; established name of the proposed product, proposed indication of use, dosage form, route of administration, strength, unit of measure, dosage units, recommended dose, typical quantity or volume, frequency of administration, product packaging, storage conditions, patient population, and prescriber population. DMEPA considers how these product characteristics may or may not be present in communicating a product name throughout the medication use system. Because drug name confusion can occur at any point in the medication use process, DMEPA considers the potential for confusion throughout the entire U.S. medication use process, including drug procurement, prescribing and ordering, dispensing, administration, and monitoring the impact of the medication.⁴

The DMEPA considers the spelling of the name, pronunciation of the name when spoken, and appearance of the name when scripted. DMEPA compares the proposed proprietary name with the proprietary and established name of existing and proposed drug products and names currently under review at the FDA. DMEPA compares the pronunciation of the proposed proprietary name with the pronunciation of other drug names because verbal communication of medication names is common in clinical settings. DMEPA examines the phonetic similarity using patterns of speech. If provided, DMEPA will consider the Sponsor's intended pronunciation of the proprietary name. However, DMEPA also considers a variety of pronunciations that could occur in the English language because the Sponsor has little control over how the name will be spoken in clinical practice. The orthographic appearance of the proposed name is evaluated using a number of different handwriting samples. DMEPA applies expertise gained from root-cause analysis of postmarketing medication errors to identify sources of ambiguity within the name that could be introduced when scripting (e.g., "T" may look like "F," lower case 'a' looks like a lower case 'u,' etc). Additionally, other orthographic attributes that determine the overall appearance of the drug name when scripted (see Table 1 below for details).

⁴ Institute of Medicine. Preventing Medication Errors. The National Academies Press: Washington DC. 2006.

Table 1. Criteria Used to Identify Drug Names that Look- or Sound-Similar to a Proposed Proprietary Name.

Type of Similarity	Considerations when Searching the Databases		
	<i>Potential Causes of Drug Name Similarity</i>	<i>Attributes Examined to Identify Similar Drug Names</i>	<i>Potential Effects</i>
Look-alike	Similar spelling	Identical prefix Identical infix Identical suffix Length of the name Overlapping product characteristics	<ul style="list-style-type: none"> Names may appear similar in print or electronic media and lead to drug name confusion in printed or electronic communication Names may look similar when scripted and lead to drug name confusion in written communication
	Orthographic similarity	Similar spelling Length of the name/Similar shape Upstrokes Down strokes Cross-strokes Dotted letters Ambiguity introduced by scripting letters Overlapping product characteristics	<ul style="list-style-type: none"> Names may look similar when scripted, and lead to drug name confusion in written communication
Sound-alike	Phonetic similarity	Identical prefix Identical infix Identical suffix Number of syllables Stresses Placement of vowel sounds Placement of consonant sounds Overlapping product characteristics	<ul style="list-style-type: none"> Names may sound similar when pronounced and lead to drug name confusion in verbal communication

Lastly, DMEPA considers the potential for the proposed proprietary name to inadvertently function as a source of error for reasons other than name confusion. Post-marketing experience has demonstrated that proprietary names (or components of the proprietary name) can be a source of error in a variety of ways. Consequently, DMEPA considers and evaluates these broader safety implications of the name throughout this assessment and the medication error staff provides additional comments related to the

safety of the proposed proprietary name or product based on professional experience with medication errors.

1. Database and Information Sources

DMEPA searches the internet, several standard published drug product reference texts, and FDA databases to identify existing and proposed drug names that may sound-alike or look-alike to the proposed proprietary name. A standard description of the databases used in the searches is provided in the reference section of this review. To complement the process, the DMEPA uses a computerized method of identifying phonetic and orthographic similarity between medication names. The program, Phonetic and Orthographic Computer Analysis (POCA), uses complex algorithms to select a list of names from a database that have some similarity (phonetic, orthographic, or both) to the trademark being evaluated. Lastly, DMEPA reviews the USAN stem list to determine if any USAN stems are present within the proprietary name. The individual findings of multiple safety evaluators are pooled and presented to the CDER Expert Panel. DMEPA also evaluates if there are characteristics included in the composition that may render the name unacceptable from a safety perspective (abbreviation, dosing interval, etc.).

2. Expert Panel Discussion

DMEPA gathers CDER professional opinions on the safety of the proposed product and discussed the proposed proprietary name (Expert Panel Discussion). The Expert Panel is composed of Division of Medication Errors Prevention (DMEPA) staff and representatives from the Office of Prescription Drug Promotion (OPDP). We also consider input from other review disciplines (OND, ONDQA/OBP). The Expert Panel also discusses potential concerns regarding drug marketing and promotion related to the proposed names.

The primary Safety Evaluator presents the pooled results of the database and information searches to the Expert Panel for consideration. Based on the clinical and professional experiences of the Expert Panel members, the Panel may recommend additional names, additional searches by the primary Safety Evaluator to supplement the pooled results, or general advice to consider when reviewing the proposed proprietary name.

3. FDA Prescription Simulation Studies

Three separate studies are conducted within the Centers of the FDA for the proposed proprietary name to determine the degree of confusion of the proposed proprietary name with marketed U.S. drug names (proprietary and established) due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. The studies employ healthcare professionals (pharmacists, physicians, and nurses), and attempts to simulate the prescription ordering process. The primary Safety Evaluator uses the results to identify orthographic or phonetic vulnerability of the proposed name to be misinterpreted by healthcare practitioners.

In order to evaluate the potential for misinterpretation of the proposed proprietary name in handwriting and verbal communication of the name, inpatient medication orders and/or outpatient prescriptions are written, each consisting of a combination of marketed and unapproved drug products, including the proposed name. These orders are optically

scanned and one prescription is delivered to a random sample of participating health professionals via e-mail. In addition, a verbal prescription is recorded on voice mail. The voice mail messages are then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants record their interpretations of the orders which are recorded electronically.

4. Comments from Other Review Disciplines

DMEPA requests the Office of New Drugs (OND) and/or Office of Generic Drugs (OGD), ONDQA or OBP for their comments or concerns with the proposed proprietary name, ask for any clinical issues that may impact the DMEPA review during the initial phase of the name review. Additionally, when applicable, at the same time DMEPA requests concurrence/non-concurrence with OPDP's decision on the name. The primary Safety Evaluator addresses any comments or concerns in the safety evaluator's assessment.

The OND/OGD Regulatory Division is contacted a second time following our analysis of the proposed proprietary name. At this point, DMEPA conveys their decision to accept or reject the name. The OND or OGD Regulatory Division is requested to provide any further information that might inform DMEPA's final decision on the proposed name.

Additionally, other review disciplines opinions such as ONDQA or OBP may be considered depending on the proposed proprietary name.

5. Safety Evaluator Risk Assessment of the Proposed Proprietary Name

The primary Safety Evaluator applies his/her individual expertise gained from evaluating medication errors reported to FDA, considers all aspects of the name that may be misleading or confusing, conducts a Failure Mode and Effects Analysis, and provides an overall decision on acceptability dependent on their risk assessment of name confusion. Failure Mode and Effects Analysis (FMEA) is a systematic tool for evaluating a process and identifying where and how it might fail.⁵ When applying FMEA to assess the risk of a proposed proprietary name, DMEPA seeks to evaluate the potential for a proposed proprietary name to be confused with another drug name because of name confusion and, thereby, cause errors to occur in the medication use system. FMEA capitalizes on the predictable and preventable nature of medication errors associated with drug name confusion. FMEA allows the Agency to identify the potential for medication errors due to orthographically or phonetically similar drug names prior to approval, where actions to overcome these issues are easier and more effective than remedies available in the post-approval phase.

In order to perform an FMEA of the proposed name, the primary Safety Evaluator must analyze the use of the product at all points in the medication use system. Because the proposed product is has not been marketed, the primary Safety Evaluator anticipates the use of the product in the usual practice settings by considering the clinical and product

⁵ Institute for Healthcare Improvement (IHI). Failure Mode and Effects Analysis. Boston. IHI:2004.

characteristics listed in Section 1.2 of this review. The Safety Evaluator then analyzes the proposed proprietary name in the context of the usual practice setting and works to identify potential failure modes and the effects associated with the failure modes.

In the initial stage of the Risk Assessment, the Safety Evaluator compares the proposed proprietary name to all of the names gathered from the above searches, Expert Panel Discussion, and prescription studies, external studies, and identifies potential failure modes by asking:

“Is the proposed proprietary name convincingly similar to another drug name, which may cause practitioners to become confused at any point in the usual practice setting? And are there any components of the name that may function as a source of error beyond sound/look-alike?”

An affirmative answer indicates a failure mode and represents a potential for the proposed proprietary name to be confused with another proprietary or established drug name because of look- or sound-alike similarity or because of some other component of the name. If the answer to the question is no, the Safety Evaluator is not convinced that the names possess similarity that would cause confusion at any point in the medication use system, thus the name is eliminated from further review.

In the second stage of the Risk Assessment, the primary Safety Evaluator evaluates all potential failure modes to determine the likely *effect* of the drug name confusion, by asking:

“Could the confusion of the drug names conceivably result in medication errors in the usual practice setting?”

The answer to this question is a central component of the Safety Evaluator’s overall risk assessment of the proprietary name. If the Safety Evaluator determines through FMEA that the name similarity would not ultimately be a source of medication errors in the usual practice setting, the primary Safety Evaluator eliminates the name from further analysis. However, if the Safety Evaluator determines through FMEA that the name similarity could ultimately cause medication errors in the usual practice setting, the Safety Evaluator will then recommend the use of an alternate proprietary name.

Moreover, DMEPA will object to the use of proposed proprietary name when the primary Safety Evaluator identifies one or more of the following conditions in the Overall Risk Assessment:

- a. OPDP finds the proposed proprietary name misleading from a promotional perspective, and the Review Division concurs with OPDP’s findings. The Federal Food, Drug, and Cosmetic Act provides that labeling or advertising can misbrand a product if misleading representations are made or suggested by statement, word, design, device, or any combination thereof, whether through a PROPRIETARY name or otherwise [21 U.S.C 321(n); See also 21 U.S.C. 352(a) & (n)].
- b. DMEPA identifies that the proposed proprietary name is misleading because of similarity in spelling or pronunciation to another proprietary or established name of a different drug or ingredient [CFR 201.10.(C)(5)].

- c. FMEA identifies the potential for confusion between the proposed proprietary name and other proprietary or established drug name(s), and demonstrates that medication errors are likely to result from the drug name confusion under the conditions of usual clinical practice.
- d. The proposed proprietary name contains an USAN (United States Adopted Names) stem.
- e. DMEPA identifies a potential source of medication error within the proposed proprietary name. For example, the proprietary name may be misleading or, inadvertently, introduce ambiguity and confusion that leads to errors. Such errors may not necessarily involve confusion between the proposed drug and another drug product but involve a naming characteristic that when incorporated into a proprietary name, may be confusing, misleading, cause or contribute to medication errors.

If DMEPA objects to a proposed proprietary name on the basis that drug name confusion could lead to medication errors, the primary Safety Evaluator uses the FMEA process to identify strategies to reduce the risk of medication errors. DMEPA generally recommends that the Sponsor select an alternative proprietary name and submit the alternate name to the Agency for review. However, in rare instances FMEA may identify plausible strategies that could reduce the risk of medication error of the currently proposed name. In that instance, DMEPA may be able to provide the Sponsor with recommendations that reduce or eliminate the potential for error and, thereby, would render the proposed name acceptable.

In the event that DMEPA objects to the use of the proposed proprietary name, based upon the potential for confusion with another proposed (but not yet approved) proprietary name, DMEPA will provide a contingency objection based on the date of approval. Whichever product, the Agency approves first has the right to use the proprietary name, while DMEPA will recommend that the second product to reach approval seek an alternative name.

The threshold set for objection to the proposed proprietary name may seem low to the Applicant/Sponsor. However, the safety concerns set forth in criteria a through e above are supported either by FDA regulation or by external healthcare authorities, including the Institute of Medicine (IOM), World Health Organization (WHO), the Joint Commission, and the Institute for Safe Medication Practices (ISMP). These organizations have examined medication errors resulting from look- or sound-alike drug names, confusing, or misleading names and called for regulatory authorities to address the issue prior to approval. Additionally, DMEPA contends that the threshold set for the Proprietary Name Risk Assessment is reasonable because proprietary drug name confusion is a predictable and preventable source of medication error that, in many instances, the Agency and/or Sponsor can identify and rectify prior to approval to avoid patient harm.

Furthermore, post-marketing experience has demonstrated that medication errors resulting from drug name confusion are notoriously difficult to rectify post-approval. Educational and other post-approval efforts are low-leverage strategies that have had limited effectiveness at alleviating medication errors involving drug name confusion. Sponsors have undertaken higher-leverage strategies, such as drug name changes, in the

past but at great financial cost to the Sponsor and at the expense of the public welfare, not to mention the Agency's credibility as the authority responsible for approving the error-prone proprietary name. Moreover, even after Sponsors' have changed a product's proprietary name in the post-approval phase, it is difficult to eradicate the original proprietary name from practitioners' vocabulary, and as a result, the Agency has continued to receive reports of drug name confusion long after a name change in some instances. Therefore, DMEPA believes that post-approval efforts at reducing name confusion errors should be reserved for those cases in which the potential for name confusion could not be predicted prior to approval.

Appendix B: Letters and Letter Strings with Possible Orthographic or Phonetic Misinterpretation

Letters in Name, Alevé PM	Scripted May Appear as	Spoken May Be Interpreted as
A	C, H, O	Ah, e, o
a	c, e, o, u	Ah, e, o
l	f, i, t, ll	r, ll
e	a, c, i, o, u	Any vowel, y
v	c, u	f
e	a, c, i, o, u	Any vowel, y
P	B, D, R	B
M	B, N, W, m, nu, nv	N
Letter strings		
al-	d	
-le-	b, h	
-ve	m, w	

Appendix C: Prescription Simulation Samples and Results

Figure 1. Aleve PM Study (Conducted on April 15, 2013)

Handwritten Medication Order	Verbal Prescription
<p><u>Medication Order:</u></p> <p><i>Aleve PM 2PO HS PM</i></p>	<p>Aleve PM</p> <p>Use as directed</p> <p>The quantity to dispense is number 40</p>
<p><u>Outpatient Prescription:</u></p> <p><i>Aleve PM</i></p> <p><i>UAD</i></p> <p><i># 40</i></p>	

FDA Prescription Simulation Responses (Aggregate 1 Rx Studies Report)

190 People Received Study
51 People Responded

Study Name: Aleve PM

Total	19	17	15		
INTERPRETATION	OUTPATIENT	VOICE	INPATIENT	TOTAL	
ALENE PM	0	0	1	1	
ALEVE	0	0	1	1	
ALEVE DM	0	1	0	1	
ALEVE PM	19	11	10	40	
ALEVE RM	0	0	1	1	
ALEVE-PM	0	1	0	1	
ALIEVE PM	0	1	0	1	
ALLEVE PM	0	2	1	3	
ALLIEVE PM	0	1	0	1	
ATENE PM	0	0	1	1	

Appendix D: Proprietary names not likely to be confused or not used in usual practice settings for the reasons described.

No.	Proprietary Name	Active Ingredient	Similarity to Aleve PM	Failure preventions
1.	Acova	Argatroban	Look	The pair has sufficient orthographic and/or phonetic differences. Additionally, no medication error reports were noted between Aleve and this name from post-marketing surveillance and our FAERS search.
2.	Adoxa	Doxycycline	Look	The pair has sufficient orthographic and/or phonetic differences. Additionally, no medication error reports were noted between Aleve and this name from post-marketing surveillance and our FAERS search.
3.	Advil PM	Ibuprofen/ Diphenhydramine	Look	The pair has sufficient orthographic and/or phonetic differences. Additionally, although the proposed name “Aleve PM” shares the “PM” modifier with Advil PM, there were no reports of confusion between the root names “Aleve” and “Advil” from our FAERS search.
4.	Alavert	Loratadine	Look	The pair has sufficient orthographic and/or phonetic differences. Additionally, no medication error reports were noted between Aleve and this name from post-marketing surveillance and our FAERS search.
5.	(b) (4)	(b) (4)	Look	(b) (4)

No.	Proprietary Name	Active Ingredient	Similarity to Aleve PM	Failure preventions
6.	Alera	Hydroquinone	Look	The pair has sufficient orthographic and/or phonetic differences. Additionally, no medication error reports were noted between Aleve and this name from post-marketing surveillance and our FAERS search.
7.	Alesse	Levonorgestrel/ Ethinyl Estradiol	Look	The pair has sufficient orthographic and/or phonetic differences. Additionally, no medication error reports were noted between Aleve and this name from post-marketing surveillance and our FAERS search.
8.	Alexin	Cephalexin	Look	Name was identified from Lexi-Comp as an international brand name for Cephalexin. However, the US brand name is Keflex. Keflex and Aleve PM has sufficient orthographic and/or phonetic differences.
9.	Allegra D	Fexofenadine/ Pseudoephedrine	Look	The pair has sufficient orthographic and/or phonetic differences. Additionally, no medication error reports were noted between Aleve and this name from post-marketing surveillance and our FAERS search.
10.	(b) (4)		Look	The pair has sufficient orthographic and/or phonetic differences.
11.	Alora	Estradiol	Look	The pair has sufficient orthographic and/or phonetic differences. Additionally, no medication error reports were noted between Aleve and this name from post-marketing surveillance and our FAERS search.

No.	Proprietary Name	Active Ingredient	Similarity to Aleve PM	Failure preventions
12.	Aloxi*** <OSE RCM# 2008-965>	Palonosetron	Look	The pair has sufficient orthographic and/or phonetic differences.
13.	Altace	Ramipril	Look	The pair has sufficient orthographic and/or phonetic differences. Additionally, no medication error reports were noted between Aleve and this name from post-marketing surveillance and our FAERS search.
14.	Aluvea	Urea	Look	The pair has sufficient orthographic and/or phonetic differences. Additionally, no medication error reports were noted between Aleve and this name from post-marketing surveillance and our FAERS search.
15.	Ativan	Lorazepam	Look	The pair has sufficient orthographic and/or phonetic differences. Additionally, no medication error reports were noted between Aleve and this name from post-marketing surveillance and our FAERS search.
16.	Tofranil PM	Imipramine Pamoate	Look	The pair has sufficient orthographic and/or phonetic differences. Additionally, no medication error reports were noted between Aleve and this name from post-marketing surveillance and our FAERS search.
17.	Uloric	Febuxostat	Look	The pair has sufficient orthographic and/or phonetic differences. Additionally, no medication error reports were noted between Aleve and this name from post-marketing surveillance and our FAERS search.

No.	Proprietary Name	Active Ingredient	Similarity to Aleve PM	Failure preventions
18.	Verelan PM	Verapamil HCl	Look	The pair has sufficient orthographic and/or phonetic differences. Additionally, no medication error reports were noted between Aleve and this name from post-marketing surveillance and our FAERS search.
19.	Aleve	Naproxen Sodium	Look & Sound	We are not aware of any name confusion within the Aleve brand product line from post-marketing surveillance and FAERS searches. The modifier “PM” provides distinction between these names.
20.	(b) (4)	(b) (4)	Look & Sound	We are not aware of any name confusion within the Aleve brand product line from post-marketing surveillance and FAERS searches. The modifiers “PM” and (b) (4) provide distinction between these names.
21.	Aleve-D Sinus & Cold	Naproxen Sodium/ Pseudoephedrine HCl	Look & Sound	We are not aware of any name confusion within the Aleve brand product line from post-marketing surveillance and FAERS searches. The modifiers “PM” and “D Sinus & Cold” provide distinction between these names.
22.	(b) (4)	Naproxen Sodium/ Pseudoephedrine HCl	Look & Sound	We are not aware of any name confusion within the Aleve brand product line from post-marketing surveillance and FAERS searches. The modifiers “PM” and (b) (4) provide distinction between these names.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CHI-MING TU
06/21/2013

CAROL A HOLQUIST on behalf of TODD D BRIDGES
06/21/2013
Signing on behalf of Todd Bridges

CAROL A HOLQUIST
06/21/2013