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RESEARCH**

APPLICATION NUMBER:

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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: September 14, 2011

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Drug Name(s) & Strength: Advil Allergy & Congestion Relief
(Ibuprofen, Chlorpheniramine Maleate, and Phenylephrine HCl)
Tablets, 200 mg/4 mg/10 mg

Application Type/Number: NDA 022113

Applicant/sponsor: Pfizer Consumer Healthcare

OSE RCM #: 2011-2379

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1 INTRODUCTION

This review evaluates the proposed proprietary name, Advil Allergy & Congestion Relief, 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

On September 25, 2007, the Applicant submitted (b) (4) as the proposed proprietary name for this product. The Division of Medication Error Prevention and Analysis (DMEPA) found the proposed name unacceptable because it “appears vulnerable to name confusion with the already marketed product, Advil Allergy Sinus (Ibuprofen, Pseudoephedrine Hydrochloride, and Chlorpheniramine Maleate) and could lead to medication errors as the only difference in the two names is (b) (4). DMEPA determined (b) (4) is ambiguous and may be prone to confusion because it has been used to represent both pseudoephedrine and phenylephrine HCl and does not have a consistent meaning among consumers and healthcare professionals” (OSE RCM#2007-2497, date June 25, 2008).

The Division of Medication Error Prevention notes that the Applicant has submitted a 505(b)(2) application for that product, the application proposes to use the proprietary name “Advil Allergy and Congestion Relief”. The Applicant currently has an approved NDA 021441 with the trade name “Advil Allergy Sinus” which was approved December 19, 2002. The currently marketed product contains ibuprofen 200 mg, pseudoephedrine HCl 30 mg and chlorpheniramine maleate 2 mg. Thus this product is kept behind the pharmacy counter as a result of the Combat Methamphetamine Epidemic Act of 2005. The proposed product “Advil Allergy & Congestion Relief” will utilize phenylephrine HCl 10 mg as the nasal decongestant ingredient. In addition, the products will also differ in the amount of chlorpheniramine maleate. The proposed product, Advil Allergy & Congestion Relief, contains 4 mg of chlorpheniramine maleate.

1.2 PRODUCT INFORMATION

Advil Allergy & Congestion Relief is an over-the-counter combination product containing ibuprofen 200 mg, chlorpheniramine maleate 4 mg, and phenylephrine HCl 10 mg per tablet. The product is indicated for the following symptoms associated with hay fever or other respiratory allergies and common cold: runny nose, itchy and watery eyes, itching of the nose or throat, sneezing, nasal congestion, sinus pressure, headache, minor aches and pains and fever. The recommended dose is one caplet every four hours while symptoms occur. Patients should not use more than six caplets in any 24-hour period. Advil Allergy & Congestion Relief will be supplied in cartons of 10 count, 20 count, and 40 count containing either one, two, or four 10 count blister cards, respectively, Piggy Back carton of 10 count, and Dispenser Bin 1s X 50 count. Table 1 on page 2 details the currently approved and marketed Advil product line.

Table 1: Currently Marketed Advil Products

Drug name	Active ingredients	Dosing Frequency
Advil	Ibuprofen 200 mg tablets/caplets/gel caps	One (or two) every 4 to 6 hours as needed
Advil Allergy Sinus	Ibuprofen 200 mg Pseudoephedrine HCl 30 mg Chlorpheniramine maleate 2 mg caplets	One caplet every 4 to 6 hours while symptoms persist
Advil Cold & Sinus	Ibuprofen 200 mg Pseudoephedrine HCl 30 mg caplets	One (or two) caplets every 4 to 6 hours while symptoms persist
Advil Liqui-Gels	Solubilized Ibuprofen 200 mg capsules	One (or two) capsules every 4 to 6 hours while symptoms persist
Advil Migraine	Solubilized Ibuprofen 200 mg capsules	Two capsules for migraine (not to exceed 2 capsules in 24 hours)
Advil PM	Ibuprofen 200 mg, Diphenhydramine citrate 38 mg caplets	Two caplets at bedside (not to exceed 2 capsules in 24 hours)
Advil Congestion Relief	Ibuprofen 200 mg, Phenylephrine HCl 10 mg tablets	One tablet every 4 hours while symptoms persist
Children's Advil Suspension	Ibuprofen 100 mg/5 mL suspension	Dosed per weight/age every 6-8 hours if needed
Junior Strength Advil Junior Strength Advil Chewables	Ibuprofen 100 mg tablet	Dosed per weight/age every 6-8 hours if needed
Infant's Advil Concentrated Drops	Ibuprofen 50 mg/1.25 mL	Dosed per weight/age every 6-8 hours if needed

2 RESULTS

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

2.1 PROMOTIONAL ASSESSMENT

DDMAC determined the proposed name is acceptable from a promotional perspective. DMEPA and the Division of Nonprescription Clinical Evaluation and the Division of Nonprescription Regulation Development concurred with the findings of DDMAC's promotional assessment of the proposed name.

2.2 SAFETY ASSESSMENT

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

2.2.1 United States Adopted Names (USAN) SEARCH

The United States Adopted Name (USAN) stem search conducted on August 12, 2011 identified that a USAN stem is present in the proposed proprietary name. The stem -gest-, is present in the word Congestion. The stem is used to represent progestins.

2.2.2 Use of “Allergy” and “Congestion Relief” Modifiers

As part of our FMEA we evaluated the potential for medication errors to occur due to misinterpretation of the modifiers “Allergy” and “Congestion Relief”.

2.2.3 FDA Adverse Event Reporting System (AERS) Selection of Cases

Since the root name Advil is currently marketed in the United States, DMEPA conducted a search of the AERS database to evaluate if confusion has occurred with the root name Advil. We also conducted a separate search of ‘Advil Congestion Relief to try to capture any safety issues with the modifier.

The reports identified through the FDA Adverse Event Reporting System (AERS) database were manually reviewed to group duplicate reports into cases and to determine if medication errors occurred. Those cases that did not describe a medication error were excluded from further analysis. For cases describing a medication error, we reviewed the cases to identify factors that contributed to the errors, and to ascertain if these risks might apply to the proposed proprietary name Advil Response.

The AERS search conducted on July 20, 2011, used the following search terms: MedDRA High Level Group Terms (HLGT): “Medication Errors”, High Level Term (HLT): “Product Label Issues”, and Preferred Term (PT): “Product Quality Issue” along with the Trade Name “Advil” and verbatim term “Advi%”. A date limit of February 1, 2011 to July 20, 2011 was used because a previous review evaluated AERS cases through January 31, 2011.

Our search retrieved 12 cases; however, the nomenclature did not contribute to any of the reported medication errors and thus not considered further in this proposed name evaluation

The AERS search conducted on September 9, 2011, used the following search terms: MedDRA High Level Group Terms (HLGT): “Medication Errors”, High Level Term (HLT): “Product Label Issues”, and Preferred Term (PT): “Product Quality Issue” along with the Trade Name “Advil Congestion Relief” and verbatim term “Advil Congestion Reli%” This search retrieved zero cases.

2.2.4 FDA Name Simulation Studies

Twenty-five practitioners responded to DMEPA’s prescription studies. None of the responses overlapped with existing marketed products. Six participants interpreted the name correctly, including the use of the abbreviation “&” in the name. Additionally, ten participants interpreted the name correctly, but using the word “and” instead of the intended abbreviation “&”. Three participants, one on each study, omitted the modifier “Relief”. 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, August 11, 2011 e-mail, the Division of Nonprescription Clinical Evaluation (DNCE) and the Division of Nonprescription Regulation Development (DNRD) indicated that they have “no concerns regarding the proposed proprietary name “Advil Allergy and Congestion Relief”.

2.2.6 Failure Mode and Effects Analysis of Similar Names

Table 2 lists the names with orthographic, phonetic, or spelling similarity to the proposed proprietary name, Advil Allergy & Congestion Relief (see Appendix B). These names were identified by the primary reviewer, the Expert Panel Discussion (EPD), other review disciplines.

Table 2: Collective List of Potentially Similar Names (DMEPA, EPD and Other Disciplines)

Look Similar		Look and Sound Similar	
<i>Name</i>	<i>Source</i>	<i>Name</i>	<i>Source</i>
Adrucil	FDA	Advil	FDA
Advicor	FDA	Advil Cold and Sinus	FDA
Advair	FDA	(b) (4)	FDA
Advate	FDA	Advil Allergy Sinus	FDA
Advil Liqui-Gels	FDA	Advil Congestion Relief	FDA
Advil Migraine Liqui-Gel	FDA	(b) (4)	FDA
Advil PM	FDA		

Our analysis of the thirteen names contained in Table 2 considered the information obtained in the previous sections along with the product characteristics. We determined the thirteen names will not pose a risk for confusion as described in Appendices D-G.

DMEPA communicated these findings to the Division of Nonprescription Clinical Evaluation via e-mail on August 11, 2011. At that time we also requested additional information or concerns that could inform our review. Per e-mail correspondence from the Division of Nonprescription Clinical Evaluation and on September 9, 2011, they stated no additional concerns with the proposed proprietary name, Advil Allergy & Congestion Relief.

3 DISCUSSION

Advil Allergy & Congestion Relief is the proposed proprietary name for Ibuprofen, Chlorpheniramine maleate, and Phenylephrine HCl tablets. This product represents an extension of the current Advil product line. The following sections discuss our evaluation of the USAN stem in the proposed proprietary name, differentiation within the Advil product line, and the modifiers “Allergy & Congestion Relief”.

3.1 USAN STEM

We note that the modifier “Congestion” contains the USAN stem –gest-, which represents progestins. Inclusion of a USAN stem in a proprietary name typically renders a name unacceptable. However, in this case the modifier “Congestion” describes a symptom. We have no expectation that the word “Congestion” should be spelled differently to avoid containing a USAN stem. Additionally, the word congestion is used in several other over-the-counter names. Therefore, although the proposed name contains the –gest- USAN stem, we do not find this to be cause for objection in this particular circumstance.

3.2 DIFFERENTIATION WITHIN THE ADVIL PRODUCT LINE

DMEPA evaluated the proposed name “Advil Allergy & Congestion Relief” with regards to potential confusion within the Advil product line. We considered how the introduction of the proposed name “Advil Allergy & Congestion Relief” would fit within the current Advil product line listed in Table 1. We note that there are three Advil products currently marketed that make use of the ‘Allergy,’ ‘&,’ ‘Congestion,’ and ‘Relief’ modifiers independently; “Advil Allergy,” Advil Cold & Sinus,” and “Advil Congestion Relief”. However, the use of all four modifiers together, “Allergy & Congestion Relief”, is unique to the proposed product and therefore would help differentiate this name from the others within the Advil product line. This is also the only product in the Advil product line that contains all three ingredients, Ibuprofen, Chlorpheniramine Maleate, and Phenylephrine which also differentiates it from the other products.

3.3 PRECEDENCE OF MODIFIERS “ALLERGY & CONGESTION RELIEF”

We note that the proposed name includes the modifiers “Allergy & Congestion Relief” and that no data was provided to support that the modifiers would not inadvertently introduce a source of error. However, we also note that these modifiers as a whole or separately are used for other marketed nonprescription products to represent an intended use (e.g. treatment of nasal congestion, runny nose, itchy nose or throat, watery eyes, sneezing, and sinus pressure). From our searches we found that oral products intended to treat chest congestion typically contain guaifenesin or dextromethorphan or both. Oral products that are intended to treat nasal congestion typically contain phenylephrine or pseudoephedrine. There appears to be no established association with the modifiers “Allergy,” “Congestion,” or “Relief” and a particular active ingredient. However, there does appear to be consistency for use of these modifiers to describe an ailment or indication the product is intended to treat. The Applicant’s intended meaning of the modifier follows this trend because the proposed product contains Chlorpheniramine Maleate and Phenylephrine HCl, which are classified as an antihistamine for allergy relief and a nasal decongestant respectively.

We also note the use of the modifier ‘&’ in the proposed name and that it is also used in ‘Advil Cold & Sinus.’ We have precedence for the use of a symbol in a product with Allegra-D 12 Hour Allergy & Congestion (OSE RCM #2010-1056) and Allegra-D 24 Hour Allergy & Congestion (OSE RCM #2010-1057). DMEPA believes the use of this modifier will not cause confusion and may differentiate it from the currently marketed ‘Advil Congestion Relief.’

Therefore, although this Applicant has not provided data to support the use of the proposed modifiers, DMEPA believes that the use of these modifiers in the nomenclature of similar marketed products adequately supports their use for the proposed product. Thus, in

consideration of the total data available, DMEPA does not believe the modifier “Allergy & Congestion Relief” represent a safety concern.

4 CONCLUSIONS

DMEPA concludes the proposed proprietary name is acceptable from both a promotional and safety perspective. However, if any of the proposed product characteristics as stated in this review are altered, DMEPA rescinds this finding and the name must be resubmitted for review. The conclusions upon re-review are subject to change.

The proposed proprietary name, Advil Allergy & Congestion Relief, must be re-reviewed 90 days before approval of the NDA.

If you have further questions or need clarifications, please contact Cheryle Milburn, OSE project manager, at 301-796-2084

4.1 COMMENTS TO THE APPLICANT

We have completed our review of the proposed proprietary name, Advil Allergy & Congestion Relief, and have concluded that this name is acceptable.

The proposed proprietary name, Advil Allergy & Congestion Relief, will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you.

If **any** of the proposed product characteristics as stated in your June 21, 2011 submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

5 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.

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. ***Electronic online version of the FDA Orange Book***
(<http://www.fda.gov/cder/ob/default.htm>)

The FDA Orange Book provides a compilation of approved drug products with therapeutic equivalence evaluations.

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

USPTO provides information regarding patent and trademarks.

9. *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.

10. *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.

11. *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.

12. *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.

13. *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.

14. *Red Book Pharmacy's Fundamental Reference*

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

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

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

16. *Medical Abbreviations Book*

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

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 DDMAC. DDMAC 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. DDMAC 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.¹

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 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.

¹ National Coordinating Council for Medication Error Reporting and Prevention.
<http://www.nccmerp.org/aboutMedErrors.html>. Last accessed 10/11/2007.

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.² The product characteristics considered for this review appears in Appendix B1 of this review.

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).

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>
	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

² Institute of Medicine. Preventing Medication Errors. The National Academies Press: Washington DC. 2006.

Look-alike			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 Division of Drug Marketing, Advertising, and Communications (DDMAC). 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 DDMAC'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.³ 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 characteristics listed in Appendix B1 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.

³ Institute for Healthcare Improvement (IHI). Failure Mode and Effects Analysis. Boston. IHI:2004.

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. DDMAC finds the proposed proprietary name misleading from a promotional perspective, and the Review Division concurs with DDMAC’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 with Possible Orthographic or Phonetic Misinterpretation

Letters in Name, NAME	Scripted May Appear as	Spoken May Be Interpreted as
Capital 'A'	'Ci', 'Ce', 'FL', 'H', 'S'	Any vowel
lower case 'd'	'cl', 'ci'	'b', 't'
lower case 'v'	'r', 'u', 'v'	'f'
lower case 'i'	Any vowel	'e'
lower case 'l'	'b', 'e', 's', 'A', 'P', 'i'	--
lower case 'r'	's', 'n', 'e', 'v'	--
lower case 'e'	'a', 'i', 'l', 'o', 'u', 'p'	Any vowel
lower case 'g'	'q', 'j', 's'	'j'
lower case 'y'	'f', 'p', 'u', 'v', 'x', 'Z'	'e', 'i', 'u'
lower case 'n'	'm', 'u', 'x', 'r', 'h', 's'	'dn', 'gn', 'kn', 'mn', 'pn'
Capital 'C'	'A', 'G', 'L', 'O'	'Z', 'K'
Capital 'R'	'B', 'Pr', 'K'	'WR'
lower case 'o'	'a', 'c', 'e', 'u'	'Oh', any vowel
lower case 's'	'G', 'S', 'g', 'n'	'x'
lower case 't'	'l', 'r', 'f', 'x', 'A'	'd'
lower case 'f'	't', 'b'	'ph'

Appendix C: Prescription Simulation Samples and Results

Figure 1. Advil Allergy and Congestion Relief Study (Conducted on June 30, 2011)

Handwritten Requisition Medication Order	Verbal Prescription
<p>Medication Order:</p> <p><i>Advil Allergy & Congestion Relief</i></p> <hr/> <p>Outpatient Prescription:</p> <p><i>Advil Allergy & Congestion Relief #20</i> <i>One tablet by mouth every 4 hours</i></p>	<p>Advil Allergy and Congestion Relief</p> <p>#20</p> <p>One tablet by mouth every 4 hours</p>

FDA Prescription Simulation Responses

85 People Received Study

25 People Responded

Study Name: Advil Allergy and Congestion Relief

Total	9	8	8	
INTERPRETATION	INPATIENT	VOICE	OUTPATIENT	TOTAL
ADVEIL ALLERGY & CONGESTION RELIEF	0	0	1	1
ADVIL ALLERGY & CONGESTION RELIEF	3	1	2	6
ADVIL ALLERGY AND CONGESTION	1	1	1	3
ADVIL ALLERGY AND CONGESTION REILEF	0	0	1	1
ADVIL ALLERGY AND CONGESTION REL	1	0	0	1
ADVIL ALLERGY AND CONGESTION RELIEF	3	4	3	10
ADVIL ALLERGY CONGESTION AND RELIEF	0	1	0	1
ADVIL ALLERGY& CONGESTION RELIEF	1	0	0	1
ADVIL ALLERGY/CONGESTION RELIEF	0	1	0	1

Appendix D: Proposed Product (Advil Allergy & Congestion Relief) Compared to Marketed Advil Marketed Product Line (from www.advil.com; Drugs@FDA; Clinical Pharmacology; and DARRTS)

Proprietary Name	Legend Status	Active Ingredients	Formulation	Dosage Strength	Dosing Frequency and Route of Administration
Advil Allergy & Congestion Relief	OTC	Ibuprofen, Pheylephrine, and Chlorpheniramine	Tablets	Ibuprofen 200 mg Chlorpheniramine 4 mg Phenylephrine 10 mg	One caplet every 4 hours while symptoms persist. Not to exceed 6 tablets per 24 hours unless otherwise advised by physician.
Advil Cold & Sinus	OTC (behind the counter)	Ibuprofen and Pseudoephedrine HCl	Caplets And Liquid-filled capsules	200 mg/30 mg	1 caplet orally every 4 to 6 hours while symptoms persist
Advil Allergy Sinus	OTC (behind the counter)	Ibuprofen, Chlorpheniramine, and Pseudoephedrine HCl	Caplets	200 mg/2 mg/30 mg	1 caplet orally every 4 to 6 hours while symptoms persist.
Advil Congestion Relief	OTC	Ibuprofen and Phenylephrine HCl	Caplets	200 mg/10 mg	1 caplet orally every 4 hours while symptoms persist, maximum of 6 tablets in 24 hours.
Advil	OTC	Ibuprofen	Tablets Caplets Gel Caplets	200 mg	1 tablet/caplet/gel caplet orally every 4 to 6 hours while symptoms persist
Advil Liqui-Gels	OTC	Ibuprofen	Liquid-filled capsules	200 mg	1 capsule orally every 4 to 6 hours while symptoms persist
Advil PM	OTC	Ibuprofen and Diphenhydramine citrate	Caplets	200 mg/38 mg	2 caplets orally at bedtime

Advil PM Liqui-Gels	OTC	Ibuprofen/Diphenhydramine hydrochloride	Liquid-filled capsules	200 mg/ 25 mg	2 capsules orally at bedtime
Advil Migraine	OTC	Ibuprofen	Liquid-filled Capsules	200 mg	2 capsules orally with a glass of water
Children's Advil	OTC	Ibuprofen	Suspension	100 mg/ 5 mL	Per dosing chart; repeat dose every 6 to 8 hours, if needed
Children's Advil Cold	OTC (behind the counter)	Ibuprofen and pseudoephedrine hydrochloride	Suspension	100 mg/15 mg per 5 mL	Per dosing chart; repeat dose every 6 hours, if needed
Infants' Advil (same as Pediatric Advil)	OTC	Ibuprofen	Concentrated Drops	50 mg/1.25 mL	Per dosing chart; repeat dose every 6 to 8 hours, if needed

Appendix E: Names of Advil Products that are no longer marketed in the U.S.

Proprietary Name	Legend Status	Active Ingredients	Formulation	Dosage Strength	Dosing Frequency and Route of Administration
Advil Junior Strength	OTC	Ibuprofen	Tablets; Chewable Tablets	100 mg	No information
Children's Advil Allergy Sinus	OTC	Ibuprofen, Chlorpheniramine Maleate, and Pseudoephedrine HCl	Suspension	100 mg/15 mg/1 mg per 5 mL	Per dosing chart; if needed, repeat dose every 6 hours while symptoms persist

Appendix F: Names of Advil Products that are currently not marketed in the U.S.

Proprietary Name	Active Ingredient(s)	Dosage Form	Status
(b) (4)			
(b) (4)			(b) (4) DMEPA objected to name; NDA 022113 not approvable 7/25/2008
(b) (4)			
(b) (4)			(b) (4) DMEPA objected to name; NDA 022113 not approvable 7/25/2008
(b) (4)			DMEPA found name acceptable: NDA 201803 March 24, 2011
(b) (4)			

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

Appendix G: Potentially confusing names with overlap in strength, but analysis indicates low potential for confusion

Failure Mode: Name Confusion	Causes (can be multiple)	Rationale for Failure Mode Prevention
Advil Allergy & Congestion Relief (Ibuprofen, Phenylephrine, and Chlorpheniramine)	N/A	One tablet every 4 hours while symptoms persist. Not to exceed 6 tablets per 24 hours unless otherwise advised by physician.
<p>Adrucil (Fluorouracil) Injection 500 mg/10 mL, 2.5 g/50 mL, and 5 g/100 mL (50 mg/mL)</p> <p><u>Usual Dose</u> Dosages range from 300 mg/m²/day to 1000 mg/m²/day intravenously for 4 days to 5 days as a continuous infusion every 4 weeks depending on the type of cancer and additional anticancer therapy vs. radiation therapy.</p>	<p><u>Orthographic</u> Both names, Adrucil and the root name, Advil, share the letter string 'Ad-'. Additionally, the letter string '-vi-' in Advil may be scripted to appear orthographically similar to the letter string '-ru-' in Adrucil.</p>	<p>Orthographic The root name, Advil, contains 5 letters whereas the name Adrucil contains 7 letters, thus making the name Adrucil appear longer. Additionally, the letter 'l' in Advil lacks orthographic similarity with the letter string '-cil' in Adrucil when scripted. Furthermore, the presence of the modifiers 'Allergy & Congestion Relief' also helps with orthographic differentiation between the two names.</p> <p><u>Dosage Form</u> Tablet vs. Injection</p> <p><u>Usual Dose</u> 1 tablet vs. 300 mg/m²/day to 1000 mg/m²/day</p> <p><u>Route of Administration</u> Oral vs. intravenous</p> <p><u>Frequency of Administration</u> Every 4 hours vs. once daily for 4 to 5 days every 4 weeks</p>

<p>Advicor (Niacin and Lovastatin) Extended Release Tablets 500 mg/20 mg; 750 mg/20 mg; 1000 mg/20 mg; 1000 mg/40 mg</p> <p><u>Usual Dose</u> 500 mg/20 mg to 1000 mg/40 mg orally once daily</p>	<p><u>Orthographic</u> Both names share the letter string 'Advi-'</p> <p><u>Dosage Forms</u> Both products are tablets</p> <p><u>Partial Numerical Overlap in Strength and Dose</u> Advil Allergy & Congestion Relief may be dosed at strengths of Ibuprofen, Chlorpheniramine, and Phenylephrine HCl that overlaps with Advicor strengths: 20 mg, 40 mg, and 1000 mg respectively.</p> <p><u>Route of Administration</u> Oral</p>	<p><u>Orthographic</u> The letter 'l' in the root name Advil lacks orthographic similarity with the letter string '-cor' in Advicor when scripted. Additionally, the presence of the modifiers 'Allergy & Congestion Relief' also helps with orthographic differentiation between the two names.</p> <p><u>Strength</u> Advil Allergy & Congestion Relief is one combination product vs. Advicor which is a combination product with multiple strengths.</p> <p><u>Frequency of Administration</u> Every 4 hours as needed while symptoms persist vs. once daily</p>
<p>Advair (Fluticasone Propionate and Salmeterol Xinafoate) Powder for Inhalation: 100 mcg/50 mcg per actuation 250 mcg/50 mcg per actuation 500 mcg/50 mcg per actuation</p> <p><u>Usual Dose</u> One inhalation twice daily</p>	<p><u>Orthographic</u> Both names share the letter string 'Adv-'</p> <p><u>Route of Administration</u> Oral</p>	<p><u>Orthographic</u> The letter string '-il' in Advil lacks orthographic similarity with the letter string '-air' in Advair when scripted. Additionally, the presence of the modifier 'Allergy & Congestion Relief' also helps with orthographic differentiation between the two names.</p> <p><u>Dosage Form</u> Tablet vs. Powder for Inhalation</p> <p><u>Strength</u> Single vs. Multiple</p> <p><u>Frequency of Administration</u> Every 4 hours as needed while symptoms persist vs. twice daily</p>

<p>Advate (Antiemophilic Factor, human recombinant) for Injection 250 units per vial; 300 units per vial; 500 units per vial; 1000 units per vial; 1500 units per vial; 2000 units per vial</p> <p><u>Usual Dose</u> 15 Units/kg to 30 Units/kg intravenously to achieve a peak post-infusion FVIII activity concentration of 30—60% of normal is given. Administer every 12 hours to 24 hours for 3 days or more until bleeding resolves</p>	<p><u>Orthographic</u> Both names contain three upstrokes in similar positions and share the letter string ‘Adv-’.</p> <p><u>Partial Numerical Overlap in Strength and Dose</u> Advil Allergy & Congestion Relief may be dosed at strengths of Ibuprofen and Phenylephrine HCl that overlap with numerical values of Advate strengths: 200 mg vs. 2000 units and 10 mg vs. 1000 units respectively, if the strengths of the other two ingredients in Advil Allergy & Congestion Relief are omitted</p>	<p><u>Orthographic</u> The letter string ‘-il’ lacks orthographic similarity with the letter string ‘-ate’ when scripted. Additionally, the presence of the modifiers ‘Allergy & Congestion Relief’ also helps with orthographic differentiation between the two names.</p> <p><u>Dosage Forms</u> Tablet vs. Powder for Injection</p> <p><u>Dosage Units</u> Milligrams vs. Units</p> <p><u>Route of Administration</u> Oral vs. Intravenous injection</p> <p><u>Usual Dose</u> One tablet vs. 15 Units/kg to 30 Units/kg intravenously</p>
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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.

/s/

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