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:	September 22, 2011
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Drug Name(s) & Strength:	Combivent Respimat (Ipratropium Bromide and Albuterol) Inhalation Spray 20 mcg/100 mcg per actuation
Application Type/Number:	NDA 021747
Applicant/sponsor:	Boehringer Ingelheim Pharmaceuticals Inc.
OSE RCM #:	2011-2436

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1 INTRODUCTION

This review evaluates the proposed proprietary name, Combivent Respimat, 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

Combivent (NDA 020291) was approved on October 24, 1996, as a chlorofluorocarbon (CFC) metered dose inhaler (MDI).

Combiven Respimat (NDA 021747) received a CR letter on August 7, 2009 and is currently on the second review cycle. DMEPA found the proposed proprietary name acceptable in OSE RCM #2008-1954, dated February 5, 2009, and in OSE RCM #2009-534 dated June 18, 2009.

1.2 PRODUCT INFORMATION

The proposed product was developed as a propellant-free replacement in preparation for the eventual removal of the Essential Use Status of Combivent Inhalation Aerosol. Combivent Respimat is a combination of an anticholinergic and beta-adrenergic indicated for use in patients with chronic obstructive pulmonary disease (COPD) on a regular aerosol bronchodilator who continue to have evidence of bronchospasm and who require a second bronchodilator.

The Combivent Respimat cartridge has a net fill weight of 4 grams and when used with the inhaler is designed to deliver at least 120 sprays after preparation for use. When the labeled number of sprays (120) has been dispensed from the inhaler, the Respimat locking mechanism will be engaged and no more sprays can be dispensed.

The recommended dosage is one inhalation four times a day, not to exceed six inhalations in 24 hours. Each dose (1 actuation) delivers 20 mcg ipratropium bromide (monohydrate) and 100 mcg albuterol (equivalent to 120 mcg albuterol sulfate).

The proposed indication, prescribing population, dosing frequency, and route of administration remain the same as that for Combivent Inhalation Aerosol. However, the dosage is different. The insert labeling indicates that Combivent is to be administered with two inhalations four times daily whereas Combivent Respimat requires ***one*** inhalation.

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 Pulmonary, Allergy, and Rheumatology (DPARP) 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 safety evaluation.

2.2.1 United States Adopted Names (USAN) SEARCH

The United States Adopted Name (USAN) stem search conducted on August 8, 2011, identified that a USAN stem is not present in the proposed proprietary name.

2.2.2 Components of the Proposed Proprietary Name

This proposed name is comprised of the currently marketed root name Combivent plus the modifier Respimat. The applicant did not submit data to support the use of the modifier. The modifier has not been used in conjunction with other proprietary names. The modifier does not contain components (i.e., route of administration,numbers that might cause confusion etc.) nor does it look or sound similar to another drug name. A modifier is needed to distinguish this product from the currently marketed product. However, despite the addition of a modifier there is still risk that this product and the currently marketed CFC product 'Combivent' may be confused for one another because the modifier 'Respimat' may be omitted and/or overlooked and because they share the same root name. These risks are discussed in section 3 of this review.

2.2.3 Medication Error Cases

Since the root name "Combivent" is currently marketed, we conducted a search of the FDA Adverse Event Reporting System (AERS) database to identify medication errors involving Combivent. The MedDRA Higher Level Terms (HLT) "Maladministration", "Medication Errors NEC", "Medication Errors Due to Accidental Exposures", "Medication Monitoring Errors", and the Preferred Terms (PT) "Overdose", "Accidental Overdose", "Multiple Drug Overdose", "Multiple Drug Overdose Accidental", "Pharmaceutical Product Complaint", and verbatim substance name "Combiven%", tradename "Combiven%" were used as search criteria on August 8, 2011.

The reports were manually reviewed to determine if a medication error occurred. Duplicate reports were combined into cases. Cases that described a medication error were categorized by type of error. We reviewed the cases within each category to identify factors that contributed to the medication errors. If the root cause was associated with name confusion involving Combivent, the cases were considered pertinent to this review. Those cases that did not describe a medication error or did not describe an error applicable to this review (e.g. patient non-adherence, intentional overdose, adverse events, complaints regarding efficacy) were excluded from further analysis.

Our AERS search retrieved 48 cases. These cases were eliminated based on the exclusion criteria listed above.

2.2.4 FDA Name Simulation Studies

Forty-two practitioners responded to DMEPA's prescription studies. Twenty-one respondents correctly identified the name Combivent Respimat with the majority of the correct responses occurring in the inpatient studies. One respondent in the outpatient

study omitted the modifier and identified the name as Combivent. 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, July 21, 2011 e-mail, the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) responded that they had "no objections to the proposed proprietary name" at the initial phase of the name review.

2.2.6 Failure Mode and Effects Analysis of Similar Names

Table 1 lists the names with orthographic, phonetic, or spelling similarity to the proposed proprietary name, Combivent Respimat (see Appendix B). These names were identified by the primary reviewer, the Expert Panel Discussion (EPD), other review disciplines.

Table 1: Collective List of Potentially Similar Names (DMEPA, EPD and Other Disciplines)

Look Similar		Sound Similar		Look and Sound Similar	
Name	***Source***	***Name***	***Source***	***Name***	***Source***
Comtrex	FDA	Combipres	FDA	Combivent	FDA
Combigan	FDA			(b) (4)	FDA
Reserpine	FDA			Combi-Rx	FDA
Resectisol	FDA			Combivent Rescue Inhaler	FDA
Resperal-DM	FDA				
Pulmicort Respules	FDA				
Combivir	FDA				
ComBgen	FDA				
Combunox	FDA				
Resporal	FDA				
Risperdal	FDA				
(b) (4)	FDA				
Combipatch	FDA				

Our analysis of the 18 names contained in Table 1 considered the information obtained in the previous sections along with their product characteristics. We determined that 17 of the 18 names will not pose a risk for confusion as described in Appendix D and E.

However, we determined that the proposed name, Combivent Respimat could be confused with the marketed product Combivent. However, this confusion will be limited (see Discussion in Section 3).

DMEPA communicated these findings to the Division of Pulmonary, Allergy, and Rheumatology Products via e-mail on August 24, 2011. At that time we also requested additional information or concerns that could inform our review. Per e-mail correspondence from the Division of Pulmonary, Allergy, and Rheumatology Products they stated no additional concerns with the proposed proprietary name, Combivent Respimat.

3 DISCUSSION

Ipratropium bromide and Albuterol are the active ingredients in both Combivent and Combivent Respimat. Combivent Respimat is an HFA formulation that will replace the currently marketed Combivent CFC formulation by 2013. The two products will coexist on the market for some time while the CFC formulation is phased out. At this time we don't have details on the transition plans.

Most, if not all, CFC to HFA conversions have occurred while maintaining the same dose. However, the Combivent to Combivent Respimat conversion is unique because the dosing differs between the formulations. Specifically, Combivent Respimat requires one inhalation four times daily whereas the existing Combivent inhaler requires two inhalations four times daily.

Therefore, it is reasonable for the applicant to not use the traditional HFA modifier to differentiate this product from the old product. Respimat may make Health Care Providers think the product has other differences although this was not supported by any data from the applicant.

The applicant did not provide data to support the understanding of the modifier Respimat and that Respimat conveys the difference in dosing. Although this modifier is ambiguous, this is the type of nomenclature that has been employed with inhalers.

Since modifiers can be omitted or overlooked from prescriptions,[1] there is a risk that the two products can be confused. These errors would result in the patient receiving the same active drug; however, since the dosage of the products differs harm could result if the patient or caregiver is unaware of the dosing differences. A person may receive a supra- or sub-therapeutic dosage if the correct product is not dispensed.

We conducted prescription studies to simulate the prescription ordering process for Combivent Respimat. In the outpatient study, one respondent omitted the modifier, confirming that the proposed name could be interpreted as "Combivent". The confusion could be exacerbated because of their overlapping product characteristics [i.e. dosage form (inhaler), route of administration (oral), indication of use, and frequency of administration (four times daily)]. In addition, the products would be stored on the pharmacy shelf next to each other, increasing the risk of selection and dispensing errors.

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[1] Lesar TS. Prescribing Errors Involving Medication Dosage Forms. *J Gen Intern Med.* 2002; 17(8): 579-587.

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Given the past precedence and potential for confusion within the Combivent product line, we see only two alternatives to differentiating the two names from each other: 1) Adding a modifier to the root name or 2) utilizing a completely different root name, in which case the risk of duplicate therapy may increase. Thus, we acknowledge that although Combivent Respimat appears vulnerable to confusion with Combivent, the use of a modifier is a previously established precedent that may help to distinguish the two names from each other. Additionally, this confusion will be limited because the CFC Combivent will be phased out from the market by December 2013.

Additionally, the Applicant will need to inform healthcare professionals about the differences between Combivent Respimat and Combivent through its promotional materials and revisions in labeling. We should do an article as well to highlight differences in the HFA and CFC versions.

4 CONCLUSIONS

The proposed name, Combivent Respimat is acceptable. 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, Combivent Respimat, must be re-reviewed upon 90 days before approval of the NDA.

Due to the differences in dosing, the Applicant and the FDA should educate healthcare professionals about these product differences. We recommend including the statement 'New Dose' on Combivent Respimat's product labels for at least 6 months after the discontinuation of Combivent. We also recommend writing an article either through Drug Topics or ISMP on the dosing differences.

If you have further questions or need clarifications, please contact Nichelle Rashid, OSE project manager, at 301-796-3904

4.1 COMMENTS TO THE APPLICANT

We have completed our review of the proposed proprietary name, Combivent Respimat, and have concluded that this it is acceptable.

The proposed proprietary name, Combivent Respimat, will be re-reviewed 90 days prior to 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 24, 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. [2]

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.

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[2] 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.[3] 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**		
	Potential Causes of Drug Name	*Attributes Examined to Identify Similar Drug Names*	*Potential Effects*

[3] Institute of Medicine. Preventing Medication Errors. The National Academies Press: Washington DC. 2006.

	Similarity		
Look-alike	Similar spelling	Identical prefix Identical infix Identical suffix Length of the name Overlapping product characteristics	• 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	• 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	• 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 gather 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.[4] 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:

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

"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 posses 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. 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), <u>and</u> 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.

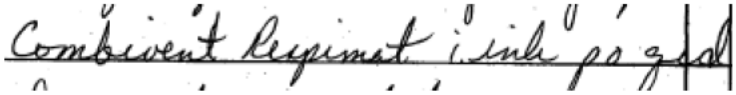
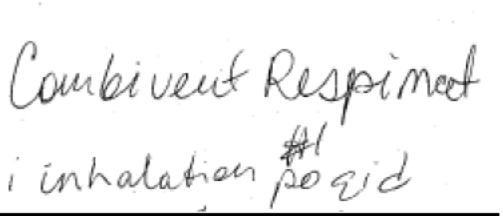
Furthermore, post-marketing experience has demonstrated that medication errors resulting from drug name confusion are notoriously difficult to rectify post-approval. Educational and other post-approval efforts are low-leverage strategies that have had limited effectiveness at alleviating medication errors 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 'C'	'A','G','L','O'	'Z','K','
lower case 'o'	Any vowel	oh
lower case 'm'	'rn','nn','n','v','w','wi','vi','onc','z'	
lower case 'b'	'l','h','k	'p','v','d'
lower case 'i'	'l','t', and any vowel	
lower case 'v'	'r','u'	'f'
lower case 'e'	'l','p', any vowel	Any vowel
lower case 'n'	'm','u','x','r','h','s'	'dn','gn,'kn','mn','pn'
lower case 't'	'r','f','x','A'	'd'
Capital 'R'	'B','Pr','K'	'Wr'
lower case 's'	'G','g','5','n'	'x'
lower case 'p'	'ys','yn','g','i','l','q'	'b'
lower case 'a'	'ci','cl','d', and any vowel	Any vowel

Appendix C: Prescription Simulation Samples and Results

Figure 1. Combivent Respimat Study (Conducted on July 15, 2011)

Handwritten Requisition Medication Order	Verbal Prescription
Medication Order: 	Combivent Respimat #1 One inhalation by mouth four times a day
Outpatient Prescription: 	

FDA Prescription Simulation Responses.

Study Name: Combivent Respimat

85 People Received Study

43 People Responded

Study Name: Combivent Respimat

Total 15 16 12

INTERPRETATION	INPATIENT	VOICE	OUTPATIENT	TOTAL
COMBIVENT	0	0	1	1
COMBIVENT RESPAMAT	0	2	0	2
COMBIVENT RESPAMET	0	2	0	2
COMBIVENT RESPIMAT	13	3	6	22
COMBIVENT RESPIMET	0	6	1	7
COMBIVENT RESPINAL	0	0	1	1
COMBIVENT RESPINAT	1	0	3	4
COMBIVENT RESPIRMAT	1	0	0	1
COMBIVENT RISPAMAT	0	1	0	1
COMBRIVENT RESPAMET	0	1	0	1
COMVAMENT RESPAMATE	0	1	0	1

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

Proprietary Name	Active Ingredient	Similarity to Name of drug	Failure preventions
Reserpine	Reserpine	Look	Lack convincing orthographic similarities
Resectisol	Mannitol	Look	Lack convincing orthographic similarities
Risperdal	Risperdone	Look	Lack convincing orthographic similarities
Resporal	Dexbrompheniramine and Pseudoephedrine Sulfate	Look	Application withdrawn on August 27, 1992 with no generics available
Resperal-DM	Brompheniramine Maleate, Dextromethorphan, Pseudoephedrine	Look and Sound	Lack convincing orthographic and phonetic similarities
			(b) (4)
Combivent Rescue Inhaler	Ipratropium and Albuterol	Look and Sound	Found on google but it is referring to the currently marketed 'Combivent' as a rescue inhaler. Not marketed as 'Combivent Rescue Inhaler'
Combipres	Chlorthalidone and Clonidine	Sound	Discontinued with a 'branded' generic available. Lacks convincing phonetic similarities
ComBi Rx	Calcium, B12, B6, Folic Acid	Look and Sound	Discontinued with only 'branded' generics available

Appendix E: Risk of medication errors due to product confusion minimized by dissimilarity of the names and/ or use in clinical practice for the reasons described.

Combivent Respimat	**20 mcg/100 mcg**	**One inhalation by mouth four times a day**
Failure Mode: Incorrect Product Ordered/ Selected/Dispensed or Administered because of Name confusion	**Causes (could be multiple)**	**Prevention of Failure Mode**
Combigan (Brimonidine tartrate and Timolol maleate) solution 0.2 %/0.5 % Usual Dose One drop into the affected eye(s) twice daily	Orthographic Both begin with the letter string 'Combi'	Orthographic The ending 'vent' vs. the ending 'igan' helps with orthographic differentiation between the two names. Dose and Dosage Form One puff vs. One drop Inhalation Spray vs. Ophthalmic Solution Route of Administration Oral vs. Opthalmic Frequency of Administration Four times a day vs. Twice a day
Comtrex (Acetaminophen, Dextromethorphan and Phenylephrine) Caplets 325 mg/10 mg/5 mg Usual Dose Two caplets by mouth every 4 hours	Orthographic Both begin with the letter string 'Com' Route of Administration Oral	Orthographic The ending 'vent' vs. the ending 'trex' helps with orthographic differentiation between the two names. Dose and Dosage Form One inhalation vs. Two caplets Inhalation Spray vs. Caplets Frequency of Administration Four times a day vs. Six times a day
Combivir (Lamivudine and Zidovudine) Tablets 150 mg/30 mg Usual Dose One tablet by mouth twice a day	Orthographic Both begin with the letter string 'Combiv' Route of Administration Oral `	Orthographic The ending 'ent' vs. the ending 'ir' helps with orthographic differentiation between the two names Dosage Form Inhalation Spray vs. Tablet Frequency of Administration Four times a day vs. Twice a day

Pulmicort Respules (Budesonide) Inhalation Suspension 0.25 mg/2 ml, 0.5 mg/2 ml, and 1 mg/2 ml Usual Dose 0.25 mg to 0.5 mg twice a day or 0.5 mg to 1 mg once daily	Orthographic Both have modifiers that begin with the same letter string, 'Resp'. Both Root names have nine letters. Route of Administration Oral	Orthographic The beginning letter strings of the root names, 'Comb' and 'Pulm' look different when scripted. Strengths Single vs. Multiple Frequency of Administration Four times a day vs. One to two times a day
Combunox (Ibuprofen and Oxycodone) 400 mg/5 mg Usual Dose One tablet every six hours as needed	Orthographic Both begin with the letter string 'Comb' Route of Administration Oral	Orthographic The ending 'vent' vs. the ending 'unox' helps with orthographic differentiation between the two names. Dosage Form Inhalation Spray vs. Tablet Rx Schedule Schedule 6 which would be kept on the shelf vs. Schedule 2 which would be kept in a safe and logged in and out
Combipatch (Estradiol and Norethindrone acetate) Patch, extended release 0.62 mg/2.7 mg Usual Dose Apply one patch twice a week	Orthographic Both begin with the letter string 'Combi'	Orthographic The ending 'vent' vs. the ending 'patch' helps with orthographic differentiation between the two names Dosage Form Inhalation Spray vs. Patch Route of Administration Oral vs. Topical Frequency of Administration Four times a day vs. Twice a week
[redacted]		(b) (4)
ComBgen (Cyanocobalamin, Folic Acid, Pyridoxine) Tablet 500 mcg/25 mg/2.2 mg Usual dose One tablet once daily	Orthograpic Both begin with the letter string 'Combi'	Orthographic The ending 'vent' vs. the ending 'Bgen' helps with orthographic differentiation between the two names Dosage Form Inhalation Spray vs. Tablet Frequency of Administration Four times a day vs. Once a day

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/s/

LISSA C OWENS
09/22/2011

CAROL A HOLQUIST
09/22/2011

Department of Health and Human Services

Public Health Service

Food and Drug Administration

Center for Drug Evaluation and Research

Office of Surveillance and Epidemiology

Date:	June 18, 2009
To:	Badrul Chowdury, MD, Director Division of Pulmonary and Allergy Products
Through:	Kellie Taylor, PharmD, MPH, Team Leader Denise Toyer, PharmD, Deputy Director Carol Holquist, RPh, Director Division of Medication Error Prevention and Analysis (DMEPA)
From:	Cathy A. Miller, MPH, BSN, Safety Evaluator Division of Medication Error Prevention and Analysis (DMEPA)
Subject:	Proprietary Name Review
Drug Name(s):	Combivent Respimat (Ipratropium Bromide and Albuterol Sulfate) Inhalation Spray 20 mcg/100 mcg per actuation
Application Type/Number:	NDA 21-747
Applicant/Applicant:	Boehringer Ingelheim Pharmaceuticals, Inc.
OSE RCM #:	2009-534

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

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EXECUTIVE SUMMARY

This re-assessment of the proprietary name is written in response to a notification that New Drug Application (NDA 21-747) will be approved within 90 days. As discussed in our previous Combivent Respimat Proprietary Name Review, OSE #2008-1954 dated February 5, 2009, Combivent Respimat is an extension of the Combivent product line and as such, the 'Respimat' modifier was proposed along with the proprietary name 'Combivent' to minimize the risk of confusion between the products. The Division of Medication Error Prevention and Analysis (DMEPA) evaluated the modifier and concluded that it will help to distinguish the proposed name, Combivent Respimat from Combivent. We also found that this distinction is especially important since each product has a different dosage (two inhalations versus one inhalation). Therefore, DMEPA found the proposed proprietary name, Combivent Respimat, acceptable. Since that review, none of the Combivent Respimat product characteristics have changed that would change the decision of acceptability from a promotional or safety perspective.

During this re-review we identified six new names for their similarity to Combivent Respimat. The results of the Failure Mode Effects Analysis found that the proposed name, Combivent Respimat, is not vulnerable to name confusion that could lead to medication errors with any of the six names. Thus, the Division of Medication Error Prevention and Analysis does not object to the use of the proprietary name, Combivent Respimat, for this product.

DMEPA considers this a final review, however, if approval of the NDA is delayed beyond 90 days from the date of this review, the Division of Pulmonary and Allergy Products should notify DMEPA because the proprietary name must be re-reviewed prior to the new approval date.

1 METHODS AND MATERIALS

Appendix A describes the general methods and materials used by the Division of Medication Error Prevention and Analysis (DMEPA) when conducting a re-assessment of a proprietary name 90 days prior to approval of an application. Section 1.1 identifies the specific search criteria associated with the proposed proprietary name, Combivent Respimat.

1.1 SEARCH CRITERIA

For this review, DMEPA used the same search criteria used in OSE Review# 2008-1954. Please refer to Section 2.1.1 on Page 5 of that review for the search criteria.

2 RESULTS

2.1 DATABASE AND INFORMATION SOURCES

The searches of the databases listed in Section 5 yielded a total of four names as having some similarity to the name Combivent Respimat. All four of the names were thought to look like Combivent Respimat. Those names include ComBgen, Combunox, Pulmicort Respules and Respi-Oil.

Additionally, DMEPA staff did not identify any United States Adopted Names (USAN) stems in the proposed proprietary name, as of May 11, 2009.

2.2 EXPERT PANEL DISCUSSION

The Expert Panel, as described in Appendix A reviewed the pool of names identified by DMEPA staff (See Section 1.1 above) and noted no additional names thought to have orthographic or phonetic similarity to Combivent Respimat.

DDMAC had no concerns regarding the proposed name from a promotional perspective, and did not offer any additional comments relating to the proposed name.

2.3 SAFETY EVALUATOR RISK ASSESSMENT

Independent searches by the primary Safety Evaluator resulted in two additional names which were thought to look similar to Combivent Respimat and represent a potential source of drug name confusion. These names include Cernevit and Omincef.

Thirteen names (See Appendix B) were identified in the previous Combivent Respimat proprietary name review. None of the Combivent Respimat product characteristics have changed since the previous review. Therefore, the original assessment is maintained. Please see OSE #2008-1954 for a detailed analysis of these names.

3 DISCUSSION

Six new names were evaluated for their potential similarity to the proposed name, Combivent Respimat.

Failure mode and effect analysis (FMEA) was then applied to determine if the proposed name could potentially be confused with the six names and lead to medication errors. This analysis determined that the name similarity between Combivent Respimat was unlikely to result in medication errors with any of the six products for the reasons presented in Appendices C through E.

4 CONCLUSIONS AND RECOMMENDATIONS

The Proprietary Name Risk Assessment findings indicate that the proposed name, Combivent Respimat, is not vulnerable to name confusion that could lead to medication errors. Thus, the Division of Medication Error Prevention and Analysis (DMEPA) has no objection to the proprietary name, Combivent Respimat, for this product at this time. Additionally, DDMAC does not object to the proposed name, Combivent Respimat from a promotional perspective.

DMEPA considers this a final review; however, if approval of the NDA is delayed beyond 90 days from the date of this review, the Division of Pulmonary and Allergy Products should notify DMEPA because the proprietary name must be re-reviewed prior to the new approval date.

4.1 COMMENTS TO THE DIVISION

If you have further questions or need clarifications, please contact Sean Bradley, Project Manager, at 301-796- 1332.

5 REFERENCES

5.1 PREVIOUS OSE REVIEW

#2008-1954 Combivent Respimat Proprietary Name Review dated February 5, 2009.

5.2 DATABASES

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. AMF Decision Support System [DSS]

DSS is a government database used to track individual submissions and assignments in 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. Stat!Ref (www.statref.com)

Stat!Ref contains full-text information from approximately 30 texts; it includes tables and references. Among the database titles are: Handbook of Adverse Drug Interactions, Rudolphs Pediatrics, Basic Clinical Pharmacology, and Dictionary of Medical Acronyms Abbreviations.

13. USAN Stems (http://www.ama-assn.org/ama/pub/category/4782.html)

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 potential for confusion between the proposed proprietary name and the proprietary and established names of drug products existing in the marketplace and those pending IND, NDA, BLA, and ANDA products currently under review by the Center. 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]

For the proposed proprietary name, DMEPA staff search a standard set of databases and information sources to identify names with orthographic and phonetic similarity and hold a Center for Drug Evaluation and Research (CDER) Expert Panel discussion to gather professional opinions on the safety of the proposed proprietary name.

The Safety Evaluator assigned to the Proprietary Name Risk Assessment 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 focuses on the avoidance of medication errors.

FMEA is a systematic tool for evaluating a process and identifying where and how it might fail. [2] DMEPA uses FMEA to analyze whether the drug names identified with orthographic or phonetic similarity to the proposed proprietary name could cause confusion that subsequently leads to medication errors in the clinical setting. 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.

In addition, the product characteristics provide the context for the verbal and written communication of the drug names and can interact with the orthographic and phonetic attributes of the names to increase the risk of

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

[2] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

confusion when there is overlap or, in some instances, decrease the risk of confusion by helping to differentiate the products through dissimilarity. Accordingly, the DMEPA staff considers the product characteristics associated with the proposed drug 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.

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. Because drug name confusion can occur at any point in the medication use process, DMEPA staff 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.[3] DMEPA provides the product characteristics considered for this review in section one.

The Division of Medication Error Prevention and Analysis considers the spelling of the name, pronunciation of the name when spoken, and appearance of the name when scripted. DMEPA also compares the spelling of the proposed proprietary name with the proprietary and established name of existing and proposed drug products because similarly in spelled names may have greater likelihood to sound similar to one another when spoken or look similar to one another when scripted. DMEPA staff also examines the orthographic appearance of the proposed name using a number of different handwriting samples. Handwritten communication of drug names has a long-standing association with drug name confusion. Handwriting can cause similarly and even dissimilarly spelled drug name pairs to appear very similar to one another. The similar appearance of drug names when scripted has led to medication errors. The DMEPA staff applies expertise gained from root-cause analysis of such 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). In addition, the DMEPA staff 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. If provided, DMEPA will consider the Applicant's intended pronunciation of the proprietary name. However, DMEPA also considers a variety of pronunciations that could occur in the English language because the Applicant has little control over how the name will be spoken in clinical practice.

[3] 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**		
	Potential causes of drug name similarity	*Attributes examined to identify similar drug names*	*Potential Effects*
Look-alike	Similar spelling	Identical prefix Identical infix Identical suffix Length of the name Overlapping product characteristics	• 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 Upstrokes Down strokes Cross-stokes Dotted letters Ambiguity introduced by scripting letters Overlapping product characteristics	• 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	• Names may sound similar when pronounced and lead to drug name confusion in verbal communication

Lastly, the DMEPA staff also 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 DMEPA 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 staff conducts searches of 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 using the criteria outlined in Section 2.1. Section 6 provides a standard description of the databases used in the searches. To complement the process, the DMEPA staff use 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, the DMEPA staff review 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.

2. CDER Expert Panel Discussion

DMEPA conducts an Expert Panel Discussion to gather CDER professional opinions on the safety of the proposed product and the proposed proprietary name. 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). 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 DMEPA staff to the Expert Panel for consideration. Based on the clinical and professional experiences of the Expert Panel members, the Panel may recommend the addition of 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. 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, conducts a Failure Mode and Effects Analysis, and provides an overall 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.[4] 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 Section one. 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?"***

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. If the answer to the question is no, the Safety Evaluator is not convinced that the names posses 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:

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

"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.

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 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), <u>and</u> 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.

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 is likely to recommend that the Applicant select an alternative proprietary name and submit the alternate name to the Agency for DMEPA to 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 Applicant 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. However, the safety concerns set forth in criteria a through e are supported either by FDA regulation or by external healthcare authorities, including the Institute of Medicine (IOM), World Health Organization (WHO), Joint Commission on Accreditation of Hospitals (JCOAH), and the Institute for Safe Medication Practices (ISMP). These organizations have examined medication errors resulting from look- or sound-alike drug 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 a preventable source of medication error that, in many instances, the Agency and/or Applicant 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. Applicants have undertaken higher-leverage strategies, such as drug name changes, in the past but at great financial cost to the Applicant 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 Applicants' 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. . (See Section 4 for limitations of the process).

Appendix B: **Names previously reviewed and determined not to pose a safety risk.**

Name	Name
Combigan	Respinal
Combipatch	Respirol
Combipres	RespiVent-D
Combivent	RespiVent-DF
Combivir	Resporal
Respahist	(b) (4)
RespiGam	

Appendix C: **Products with no numerical overlap in strength and dose**

Product name with potential for confusion	Similarity to Combivent Respimat	Strength	Usual Dose
Combivent Respimat		**20 mcg/100 mcg per actuation**	**One Inhalation four times daily**
Omnicef	Look-Alike	300 mg Tablets 125 mg and 250 mg Suspension	300 mg or 600 mg every twelve hours

<u>Appendix D:</u> Single strength products with multiple differentiating product characteristics

Product name with potential for confusion	**Similarity to Combivent Respimat**	**Strength**	**Usual Dose (if applicable)**	**Differentiating Product Characteristics**
Combivent Respimat		**20 mcg/100 mcg per actuation**	**One Inhalation four times daily**	**Dose expressed: 'One inhalation' or 'One puff'.** **Dosage form: Inhalation Spray** **Route of Administration: Oral Inhalation** **Frequency: Four Times Daily**
Cernevit	Look-Alike	Multivitamins	Reconstitute single dose vial in 5 mL Sterile Water and then administer intravenously.	Dose expressed: "Infuse vial after reconstitution" intravenously Dosage form: Lypholized powder for injection Route of administration: Intravenous
Respi-Oil	Look-Alike	Herbal Supplement containing Eucalyptus, Rosemary, Sage, Tea Tree and Nutmeg	Rub oil onto chest or shoulders as needed	Dose expressed: Rub onto 'area' Dosage form: Solution Route of Administration: Topical Frequency: As needed

Appendix E: Potential confusing name with similarity in drug class and administration

Failure Mode: Name confusion	**Causes (could be multiple)**	**Effect**
Combivent Respimat (Ipratropium Bromide and Albuterol Sulfate)	**20 mcg/100 mcg per actuation**	**One Inhalation four times daily**
Pulmicort Respules (Busesonide) Inhalation Suspension 0.25 mg/2mL, 0.5 mg/2 mL and 1 mg/2 mL	Orthographic similarities include 'cort' looks like 'vent'; the upstroke 'b' in Combivent can look like the upstroke 'l' in Pulmicort and is similarly placed; both names' contain two words, the second of which begins with 'Resp'.	Orthographic differences in the names, expression of usual dose and available strengths minimize the likelihood of medication error in the usual practice setting. *Rationale:* The 'P' in Pulmicort does not look like the 'C' in Combivent; the endings of the second words vary such that 'mat' does not look like 'ules' with the last letter in the word Respimat ending in an upstroke/crossstroke 't' not present in Respules, differentiating the overall appearance of the word. Pulmicort Respules is available in three different strengths which would be included on prescription orders and then strengths do not overlap numerically with Combivent Respimat which would be included on prescription orders (0.25 mg, 0.5 mg, or 1 mg versus 20 mcg) differentiating the two names.
ComBgen (Vitamin B-12, Folic Acid, Vitamin B-6) tablets	Orthographic similarities include both names begin with 'Comb' and contain the letters 'en' similarly placed.	Orthographic differences in the names, dose expression and dosage form minimize the likelihood of medication error in the usual practice setting. *Rationale:* ComBgen contains a downstroke 'g' not present in Combivent; and Combivent contains a crossstroke 't' in the last letter position not present in ComBgen, differentiating the appearances of the two names. Additionally, the modifier 'Respimat' would also differentiate the two names on prescription orders. Prescription orders for ComBgen would be written to include the dose expression of "take one" or "take one tablet" while Combivent Respimat would be written "one *inhalation*" or "one *puff*" differentiating the names.
Combunox (Oxycodone and Ibuprofen) 5 mg/400 mg tablet	Orthographic similarities include both names begin with 'Comb' and the 'n' is similarly placed in both names.	Orthographic differences in the names, dose expression and dosage form minimize the likelihood of medication error in the usual practice setting. *Rationale:* The endings of the names differ with 'nox' looking orthographically different than 'vent' with the upstroke crossstroke 't'. Additionally, the modifier 'Respimat' would also differentiate the two names on prescription

		orders. Prescription orders for Combunox would include the dose expression “take one every six hours” while Combivent Respimat dosing would be expressed “one puff” or “one inhalation” differentiating the two names.

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For Carol Holquist, Director DMEPA

Department of Health and Human Services

Public Health Service

Food and Drug Administration

Center for Drug Evaluation and Research

Office of Surveillance and Epidemiology

Date:	February 5, 2009
To:	Badrul Chowdhury, MD, Director Division of Pulmonary and Allergy Products
Thru:	Kellie Taylor, PharmD, MPH, Team Leader Denise Toyer, PharmD, Deputy Director Carol Holquist, RPh, Director Division of Medication Error Prevention and Analysis
From:	Jinhee J. Lee, PharmD, Safety Evaluator Division of Medication Error Prevention and Analysis
Subject:	Proprietary Name Review
Drug Name:	Combivent Respimat (Ipratropium Bromide and Albuterol Sulfate) Inhalation Spray 20 mcg/100 mcg per actuation
Application Type/Number:	NDA # 21-747
Applicant/Applicant:	Boehringer Ingelheim Pharmaceuticals, Inc.
OSE RCM #:	2008-1954

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EXECUTIVE SUMMARY

The Division of Medication Error Prevention and Analysis (DMEPA) evaluated the proposed proprietary name, Combivent Respimat. This product is an extension of the Combivent product line and as such, Combivent Respimat, may be confused for the existing Combivent product. To minimize the risk, the Applicant added the modifier, Respimat. We recognize the precedence of utilizing a distinct modifier to differentiate the proposed product from their existing product when a new inhaler device is first introduced. Moreover, we believe a modifier will help to distinguish the proposed name, Combivent Respimat, from Combivent. This distinction is especially important since each product has a different dosage (two inhalations versus one inhalation). Thus, DMEPA has no objections to the use of the proposed name, Combivent Respimat, for this product at this time. The Division of Pulmonary and Allergy Products (DPAP) concurs with this assessment.

Additionally, since this product is an extension of an existing product line and errors can occur upon launch of the new products, we recommend the Applicant consider informing healthcare professionals about the differences between Combivent Respimat and Combivent through its promotional materials.

1 BACKGROUND

1.1 INTRODUCTION

This review was written in response to a request from the Division of Pulmonary and Allergy Products for a final review of the proposed proprietary name, Combivent Respimat. Container/Blister labels, blister carton and insert labeling were also provided to be evaluated from a medication errors perspective. Labeling comments will be provided under a separate cover in a forthcoming review managed under the same review number (OSE 2008-1954).

1.2 REGULATORY HISTORY

Combivent Respimat (Ipratropium Bromide and Albuterol Sulfate) is an extension of the Combivent product line. Combivent (NDA 20-291) was approved on October 24, 1996, a chlorofluorocarbon (CFC) metered dose inhaler (MDI). The proposed product was developed as a propellant-free replacement in preparation for the eventual removal of the Essential Use Status of Combivent Inhalation Aerosol. The proposed indication, prescribing population, dosing frequency and route of administration remain the same as that for Combivent Inhalation Aerosol. However, the dosage is different. The insert labeling indicates that Combivent is to be administered with two inhalations four times daily whereas Combivent Respimat requires ***one*** inhalation.

1.3 PRODUCT INFORMATION

Combivent Respimat is the proposed name for Ipratropium Bromide and Albuterol Sulfate. Combivent Respimat is a combination of an anticholinergic and beta-adrenergic indicated for use in patients with chronic obstructive pulmonary disease (COPD) on a regular aerosol bronchodilator who continue to have evidence of bronchospasm and who require a second bronchodilator.

The Combivent Respimat cartridge has a net fill weight of 4 grams and when used with the inhaler, is designed to deliver at least 120 sprays after preparation for use. When the labeled number of sprays (120) has been dispensed from the inhaler, the Respimat locking mechanism will be engaged and no more sprays can be dispensed.

The recommended dosage is one inhalation four times a day, not to exceed six inhalations in 24 hours. Each dose (1 actuation) delivers 20 mcg ipratropium bromide (monohydrate) and 100 mcg albuterol (equivalent to 120 mcg albuterol sulfate).

2 METHODS AND MATERIALS

This section describes the methods and materials used by the DMEPA staff conducting a proprietary name risk assessment (see 2.1 Proprietary Name Risk Assessment). The primary focus of the assessment is to identify and remedy potential sources of medication error prior to drug approval. 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]

2.1 PROPRIETARY NAME RISK ASSESSMENT

FDA's Proprietary Name Risk Assessment considers the potential for confusion between the proposed proprietary name, Combivent Respimat, and the proprietary and established names of drug products existing in the marketplace and those pending IND, BLA, NDA, and ANDA products currently under review by CDER.

For the proprietary name, Combivent Respimat, the DMEPA staff search a standard set of databases and information sources to identify names with orthographic and phonetic similarity (see Sections 2.1.1 for detail) and held an CDER Expert Panel discussion to gather professional opinions on the safety of the proposed proprietary name (see 2.1.1.2).

The Safety Evaluator assigned to the Proprietary Name Risk Assessment is responsible for considering the collective findings, and provides an overall risk assessment of the proposed proprietary name (see detail 2.1.4). The overall risk assessment is based on the findings of a Failure Mode and Effects Analysis (FMEA) of the proprietary name, and is focused on the avoidance of medication errors. FMEA is a systematic tool for evaluating a process and identifying where and how it might fail.[2] Additionally, for this review DMEPA conducted a second Failure Mode and Effects Analysis (FMEA) to evaluate whether marketing the proposed product under the name, Combivent Respimat, or an alternate proprietary name would be less prone to medication errors. FMEA is used to analyze whether the drug names identified with look- or sound-alike similarity to the proposed name could cause confusion that subsequently leads to medication errors in the clinical setting. DMEPA uses the clinical expertise of the medication error staff to anticipate the conditions of the clinical setting that the product is likely to be used in based on the characteristics of the proposed product.

In addition, the product characteristics provide the context for the verbal and written communication of the drug names and can interact with the orthographic and phonetic attributes of the names to increase the risk of confusion when there is overlap, or, in some instances, decrease the risk of confusion by helping to differentiate the products through dissimilarity. As such, the staff considers the product characteristics associated with the proposed drug throughout the risk assessment, since 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.

Typical product characteristics considered when identifying drug names that could potentially be confused with the proposed drug name include, but are not limited to established name of the

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

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

proposed product, the proposed indication, 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. 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.[3]

2.1.1 Search Criteria

The DMEPA staff considers the spelling of the name, pronunciation of the name when spoken, and appearance of the name when scripted as outlined in Appendix A.

For this review, particular consideration was given to drug names beginning with the letter 'C' and 'R' when searching to identify potentially similar drug names, as 75% of the confused drug names reported by the USP-ISMP Medication Error Reporting Program involve pairs beginning with the same letter.[4][5]

To identify drug names that may look similar to the root name Combivent, or the modifier Respimat, the DMEPA staff also considers the other orthographic appearance of the name on lined and unlined orders. We also consider the possibility that prescriptions or orders for Combivent Respimat could be misinterpreted as representing two separate products (e.g. a prescription for "Combivent" and "Respimat" written in close proximity to one another or the modifier is omitted altogether). Specific attributes taken into consideration include the length of the name (9 letters for Combivent, 8 letters for Respimat), upstrokes (five, capital letters 'C' and 'R', and lowercase letters, 'b' and 't'), downstrokes (one, 'p'), cross-strokes (two, 't'), and dotted letters (one, 'i'). Several letters in Combivent may be vulnerable to ambiguity when scripted, including the letter 'C' may appear as 'A' or 'O'; lower case 'o' appear as a lower case 'a', 'v' as an 'n', and 't' as a 'x'. Additionally, several letters in Respimat may be vulnerable to ambiguity when scripted, including the letter 'R' may appear as 'N'; lower case 'a' appear as a lower case 'u' or 'o' and 't' like 'x'. As such, the staff should also consider these alternate appearances when identifying drug names that may look similar to Combivent Respimat.

When searching to identify potential names that may sound similar to Combivent Respimat, the DMEPA staff search for names with similar number of syllables (three and three), stresses (COM-bi-vent or com-BI-vent or com-bi-VENT and RES-pi-mat or res-PI-mat or res-pi-MAT), consonant sound pronunciation ("Cohm" versus "Calm" or "be" versus "by" or Respi" versus "Respy"), and placement of vowel and consonant sounds. In addition, several letters in Combivent may be subject to misinterpretation when spoken, including the letter "C" may be interpreted as "K" and 'm' as 'n'. Also, several letters in Respimat may be misinterpreted when spoken, including the letter "R" may be interpreted as "L", "p" as "b", and "m" as "n". As such, the staff also considers these alternate pronunciations when identifying drug names that may sound similar to Combivent Respimat. The Applicant's intended pronunciation of the proprietary name could not be expressly taken into consideration, as this was not provided with the proposed name submission.

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[3] Institute of Medicine. Preventing Medication Errors. The National Academies Press: Washington DC. 2006.

[4] Institute for Safe Medication Practices. Confused Drug name List (1996-2006). Available at http://www.ismp.org/Tools/confuseddrugnames.pdf

[5] Kondrack, G and Dorr, B. Automatic Identification of Confusable Drug Names. Artificial Intelligence in Medicine (2005)

The staff also consider the product characteristics associated with the proposed drug throughout the identification of similar drug names, since the product characteristics of the proposed drug ultimately determine the use of the product in the clinical practice setting For this review, the medication error staff were provided with the following information about the proposed product: the proposed proprietary name (Combivent Respimat), the established name (Iptratropium bromide and Albuterol Sulfate), proposed indication (for use in patients with chronic obstructive pulmonary disease on a regular aerosol bronchodilator who continue to have evidence of bronchospasm and who require a second bronchodilator), strength (20 mcg/100 mcg per actuation), dose (1 inhalation), frequency of administration (four times daily, not to exceed six inhalations in 24 hours), route (oral) and dosage form of the product (inhalation spray). Appendix A provides a more detailed listing of the product characteristics the medication error staff generally takes into consideration.

Lastly, the DMEPA staff also considers the potential for the proposed 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. As such, these broader safety implications of the name are considered and evaluated throughout this assessment and the medication error staff provides additional comments related to the safety of the proposed name or product based on their professional experience with medication errors.

2.1.1.1 Databases and Information Sources

The proposed proprietary name, Combivent Respimat, was provided to the DMEPA staff to conduct a search of 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 Combivent Respimat using the criteria outlined in 2.1.1. A standard description of the databases used in the searches is provided in Section 6.2. To complement the process, the DMEPA staff 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, the DMEPA staff reviews the USAN stem list to determine if any USAN stems are present within the proprietary name. The findings of the individual Safety Evaluators were then pooled and presented to the Expert Panel.

2.1.1.2 CDER Expert Panel Discussion

An Expert Panel Discussion is held by DMEPA to gather CDER professional opinions on the safety of the product and the proprietary name, Combivent Respimat. Potential concerns regarding drug marketing and promotion related to the proposed names are also discussed. This group is composed of the DMEPA Staff and representatives from the Division of Drug Marketing, Advertising, and Communications (DDMAC).

The pooled results of the medication error staff were presented to the Expert Panel for consideration. Based on the clinical and professional experiences of the Expert Panel members, the Panel may recommend the addition of names, additional searches by the Safety Evaluator to supplement the pooled results, or general advice to consider when reviewing the proposed proprietary name.

2.1.2 FDA Prescription Analysis Studies

Three separate studies are conducted within the Centers of the FDA for the proposed proprietary name to determine the degree of confusion of Combivent Respimat 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 a total of 122 healthcare professionals (pharmacists, physicians, and nurses), and attempts to simulate the prescription ordering process. The results are used by the Safety Evaluator to identify any orthographic or phonetic vulnerability of the proposed name to be misinterpreted by healthcare professionals.

In order to evaluate the potential for misinterpretation of Combivent Respimat in handwriting and verbal communication of the name, inpatient medication orders and outpatient prescriptions are written, each consisting of a combination of marketed and unapproved drug products, including the proposed name. These prescriptions are optically scanned and one prescription is delivered to a random sample of 122 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 send their interpretations of the orders via e-mail to the medication error staff.

Figure 1. Combivent Respimat Study (conducted on January 5, 2008)

HANDWRITTEN PRESCRIPITON AND MEDICATION ORDER	VERBAL PRESCRIPTION
Inpatient Prescription Order: Combivent Respimat #1 1 inhalation by mouth qid	Combivent Respimat #1 1 inhalation by mouth qid
Outpatient Medication Order : Combivent Respimat #1 1 inhalation by mouth four times daily	

2.1.3 Comments from the Division of Pulmonary and Allergy Products

DMEPA requests the regulatory division in the Office of New Drugs responsible for the application for their comments and concerns from a clinical perspective with regard to the proposed proprietary name at 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. Any comments or concerns are addressed in the safety evaluator's assessment.

The Review Division is contacted a second time following our analysis of the proposed name. At this point, DMEPA conveys their decision to accept or reject the name. The regulatory division is requested to concur /not concur with DMEPA's final decision.

2.1.4 Safety Evaluator Risk Assessment of the Proposed Proprietary Name

Based on the criteria set forth in Section 2.1.1, the Safety Evaluator Risk Assessment applies their individual expertise gained from evaluating medication errors reported to FDA to conduct a Failure Mode and Effects Analysis and provide an overall risk 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.[6] When applying FMEA to assess the risk of a proposed proprietary name, DMEPA seeks to evaluate the potential for a proposed name to be confused with another drug name as a result of the name confusion and 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 look- or sound-alike drug names prior to approval, where actions to overcome these issues are easier and more effective then remedies available in the post-approval phase.

In order to perform an FMEA of the proposed name, the Safety Evaluator must analyze the use of the product at all points in the medication use system. Because the proposed product is not yet marketed, the Safety Evaluator anticipates the use of the product in the usual practice settings by considering the clinical and product characteristics listed in Appendix A. 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 evaluation, and studies, and identifies potential failure modes by asking: "Is the name Combivent Respimat convincingly similar to another drug name, which may cause practitioners to become confused at any point in the usual practice setting?" An affirmative answer indicates a failure mode and represents a potential for Combivent Respimat to be confused with another proprietary or established drug name because of look- or sound-alike similarity. If the answer to the question is no, the Safety Evaluator is not convinced that the names posses similarity that would cause confusion at any point in the medication use system and the name is eliminated from further review.

In the second stage of the Risk Assessment, all potential failure modes are evaluated 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 ultimately not be a source of medication errors in the usual practice setting, the name is eliminated 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 that an alternate proprietary name be used. In rare instances, the FMEA findings may provide other risk-reduction strategies, such as product reformulation to avoid an overlap in strength or an alternate modifier designation may be recommended as a means of reducing the risk of medication errors resulting from drug name confusion.

DMEPA will object to the use of proposed proprietary name when the one or more of the following conditions are identified in the Safety Evaluator's Risk Assessment:

1. 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,

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

device, or any combination thereof, whether through a trade name or otherwise. [21 U.S.C 321(n); see also 21 U.S.C. 352(a) & (n)].

2. 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)].
3. FMEA identifies potential for confusion between the proposed proprietary name and other proprietary or established drug names, and demonstrates that medication errors are likely to result from the drug name confusion under the conditions of usual clinical practice.
4. The proposed proprietary name contains an USAN stem, particularly in a manner that is contradictory to the USAN Council's definition.
5. The DMEPA staff identifies a potential source of medication error within the proposed proprietary name. 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.

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 is awarded approval first has the right to the use the name, while DMEPA will recommend that the second product to reach approval seek an alternative name.

If none of these conditions are met, then DMEPA will not object to the use of the proprietary name. If any of these conditions are met, then DMEPA will object to the use of the proprietary name. The threshold set for objection to the proposed proprietary name may seem low to the Applicant; however, the safety concerns set forth in criteria 1 through 5 are supported either by FDA Regulation or by external healthcare authorities, including the IOM, WHO, JCAHO, and ISMP, have examined medication errors resulting from look- or sound-alike drug names and called for Regulatory Authorities to address the issue prior to approval.

Furthermore, 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, can be identified and remedied prior to approval to avoid patient harm.

Additionally, post-marketing experience has demonstrated that medication errors resulting from drug name confusion are notoriously difficult to remedy post-approval. Educational efforts and so on are low-leverage strategies that have proven to have limited effectiveness at alleviating the medication errors involving drug name confusion. Higher-leverage strategies, such as drug name changes, have been undertaken in the past; but at great financial cost to the Applicant, and at the expense of the public welfare, not to mention the Agency's credibility as the authority responsible for the approving the error-prone proprietary name. Moreover, even after Applicant's have changed a product's proprietary name in the post-approval phase, it is difficult to eradicate the original proprietary name from practitioner's vocabulary, and as such, 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 (see limitations of the process).

If DMEPA objects to a proposed proprietary name on the basis that drug name confusion could lead to medication errors, the FMEA process is used to identify strategies to reduce the risk of medication errors. DMEPA is likely to recommend that the Applicant select an alternative proprietary name and submit the alternate name to the Agency for DMEPA to review. However,

in rare instances FMEA may identify plausible strategies that could reduce the risk of medication error of the currently proposed name, and so DMEPA may be able to provide the Applicant with recommendations that reduce or eliminate the potential for error would render the proposed name acceptable.

2.2 ADVERSE EVENT REPORTING SYSTEM (AERS) DATABASE

Since the root name "Combivent" is currently marketed, we conducted a search of the Adverse Event Reporting System (AERS) database to identify any medication errors associated with the use of Seasonique. The MedDRA Higher Level Terms (HLT) "Maladministration", "Medication Errors NEC", "Medication Errors Due to Accidental Exposures", "Medication Monitoring Errors", and the Preferred Terms (PT) "Overdose", "Accidental Overdose", "Multiple Drug Overdose", "Multiple Drug Overdose Accidental", "Pharmaceutical Product Complaint", and verbatim substance name "Combiven%", tradename "Combiven%" were used as search criteria on December 8, 2008.

3 RESULTS

3.1 PROPRIETARY NAME RISK ASSESSMENT

3.1.1 Databases and Information Sources

The searches identified a total of 26 names as having some similarity to the name Combivent Respimat.

Sixteen of the 26 names were thought to look like Combivent Respimat, which include: Atrovent, Cernevit, Combavia Vitamin, CombiPatch, Combipres, Perforomist, Respahist, Respbid, Resperal, Respinal, Respir, Respirol, Respi-Tann, Respi-TannG, Resporal, and Rifamate. One name, Conivaptan, was thought to sound like Combivent Respimat. Nine names (Combigan, Combivent, Combivent Respimat, Combivent UDV, Combivir, RespiGam, Respimat, Respimex, and (b) (4) were thought to look and sound similar to Combivent Respimat.

A search of the United States Adopted Name (USAN) stem list on December 12, 2008 identified no USAN stems within the proposed name, Combivent Respimat.

3.1.2 CDER Expert Panel Discussion

The Expert Panel reviewed the pool of names identified by the DMEPA staff (see section 3.1.1. above), and commented that the drug product would potentially be ordered without the root name, Combivent, and simply as "Respimat". The Panel also commented on whether the existing product, Combivent Inhalation Aerosol, would remain on the market after Combivent Respimat was introduced.

DDMAC had no concerns regarding the proposed name from a promotional perspective, and did not offer any additional comments relating to the proposed name.

3.1.3 FDA Prescription Analysis Studies

A total of 27 practitioners responded. Only two respondents (from the voice study) interpreted both parts of the name incorrectly. The remaining responses misinterpreted the root name or the modifier. One respondent omitted the modifier altogether and one respondent interpreted the modifier as simply, 'R'. Most of the respondents interpreted the modifier correctly while the remaining responses were phonetic and orthographic variations of the proposed name, Combivent Respimat. See Appendix B for the complete listing of interpretations from the verbal and written prescription studies.

3.1.4 Comments from the Division of Pulmonary and Allergy Products

In response to the OSE January 7, 2009 e-mail, DPAP did not forward any comments on the proposed name at the initial phase of the name review.

DMEPA notified DPAP via e-mail that we had no objections to the proposed proprietary name, Combivent Respimat, on January 7, 2009. Per e-mail correspondence from the Division of Pulmonary and Allergy Products on January 12, 2009, they indicated they concur with our assessment of the proposed name, Combivent Respimat.

3.1.5 Safety Evaluator Risk Assessment of the Proposed Proprietary Name

Independent searches by the primary Safety Evaluator identified 8 additional names (Berodual Respimat, RespiVent-D, Respital, Revlimid, Risperdal, Respicort, Respimox, and Respet) that were thought to look and/or sound similar to Combivent Respimat and represent a potential source of drug name confusion.

As such, a total of 34 names were analyzed to determine if the drug names could be confused with Combivent Respimat and if the drug name confusion would likely result in a medication error.

Five of the 34 names lacked orthographic and/or phonetic similarity and were not evaluated further (Appendix C). Twenty-eight names were unlikely to result in medication errors for reasons described in Appendices D through G. The remaining name, Combivent, is discussed in section 4.1.

3.2 ADVERSE EVENT REPORTING SYSTEM (AERS) DATABASE

Our AERS search retrieved 18 cases, however, the nomenclature did not contribute to any of the reported medication errors.

4 DISCUSSION

4.1 PROPRIETARY NAME RISK ASSESSMENT

The results of the Proprietary Name Risk Assessment found that the proposed name, Combivent Respimat, is vulnerable to confusion with Combivent since both share the same root name.

Ipratropium bromide and Albuterol sulfate are the active ingredients in both Combivent and Combivent Respimat. Combivent Respimat is an addition to this product line.

DMEPA believes that the additional product will introduce name confusion and increase the opportunity for errors with the Combivent product line, particularly if the products co-exist in the marketplace together for the reasons described below.

4.1.1 Modifier Omission

The reason we believe Combivent may be confused with Combivent Respimat is that modifiers can be omitted or overlooked from prescriptions,[7] and the only difference in the nomenclature of the two inhalers is the modifier portion of the name. In the context of a medication order or prescription, we believe that this difference could be overlooked particularly when the product is first introduced, especially since the modifier follows the root name. We conducted prescription studies to simulate the prescription ordering process for Combivent Respimat. In this case, one respondent omitted the modifier, confirming that that the proposed name could be interpreted as

[7] Lesar TS. Prescribing Errors Involving Medication Dosage Forms. *J Gen Intern Med.* 2002; 17(8): 579-587.

"Combivent". The omission or oversight of the modifier on a prescription or medication order for Combivent Respimat would likely result in confusion with the existing inhaler. The confusion could be exacerbated because of their overlapping product characteristics (i.e. dosage form (inhaler), route of administration (oral), indication of use, and frequency of administration (four times daily)). In addition, the products would be stored on the pharmacy shelf next to each other, increasing the risk of selection and dispensing errors.

Although these errors could conceivably result in the patient receiving the same active drug, the dosage of the two products differs and harm could result if the patient or caregiver is unaware of the product differences. Specifically, the Respimat inhaler requires one inhalation four times daily whereas the existing inhaler, Combivent, requires two inhalations four times daily. Since the dosages are different, a person may receive a supra- or subtherapeutic dosage if the correct medication is not dispensed.

4.1.2 Modifier Ambiguity

In addition to these concerns regarding the omission or oversight of the modifier, we note that the word "Respimat" is an ambiguous term that does not have a recognized meaning among healthcare professionals and does not convey that the product is an inhaler. However, we recognize the precedence of utilizing a distinct modifier to differentiate the proposed product from their existing product when a new inhaler device is introduced. Thus, although this modifier is ambiguous, this is the type of nomenclature that has been employed with inhalers. We also find the modifier acceptable with respect to potential confusion with existing drug names because of look or sound-alike similarity

Given the past precedence and potential for confusion within the Combivent product line, we see only two alternatives to differentiating the two names from each other: 1) Adding a modifier to the root name or 2) Utilizing a completely different root name, in which case the risk of duplicate therapy may increase. Thus, we acknowledge that although Combivent Respimat appears vulnerable to confusion with Combivent, the use of a modifier is a previously established precedent that may help to distinguish the two names from each other.

Additionally, we believe that it might help to reduce the potential for confusion if the Applicant informs healthcare professionals about the differences between Combivent Respimat and Combivent through its promotional materials.

5 CONCLUSIONS AND RECOMMENDATIONS

The Proprietary Name Risk Assessment findings indicate that the proposed name, Combivent Respimat, may be confused with Combivent, but that the use of a modifier is an established precedent that may help distinguish the products from each other. This distinction is especially important since each product has a different dosage (two inhalations versus one inhalation). The Applicant should educate healthcare professionals about these product differences. DMEPA does not object to the use of the proprietary name, Combivent Respimat, for this product at this time. The Division of Pulmonary and Allergy Products concurs with this assessment.

However, if **any** of the proposed product characteristics as stated in this review are altered prior to approval of the product, DMEPA rescinds this Risk Assessment finding. If the product approval is delayed beyond 90 days from the date of this review, the proposed name must be resubmitted for evaluation.

5.1 COMMENTS TO THE DIVISION

DMEPA would appreciate feedback on the final outcome of this review. We would be willing to meet with the Division for further discussion, if needed. Please copy DMEPA on any

correspondence to the Applicant pertaining to this issue. If you have further questions or need clarifications, please contact Sean Bradley, OSE Project Manager, at 301-796-1332.

5.2 COMMENTS TO THE APPLICANT

We have completed our review of the proposed proprietary name, Combivent Respimat, and have concluded that it is acceptable.

Combivent Respimat 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 are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

6 REFERENCES

6.1 DATABASES

1. Adverse Event Reporting System (AERS)

AERS is a database application in CDER FDA that contains adverse event reports for approved drugs and therapeutic biologics. These reports are submitted to the FDA mostly from the manufactures that have approved products in the U.S. The main utility of a spontaneous reporting system that captures reports from health care professionals and consumers, such as AERS, is to identify potential postmarketing safety issues. There are inherent limitations to the voluntary or spontaneous reporting system, such as underreporting and duplicate reporting; for any given report, there is no certainty that the reported suspect product(s) caused the reported adverse event(s); and raw counts from AERS cannot be used to calculate incidence rates or estimates of drug risk for a particular product or used for comparing risk between products.

2. Micromedex Integrated Index (http://csi.micromedex.com)

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

3. Phonetic and Orthographic Computer Analysis (POCA)

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. This is a database which was created for the Division of Medication Error Prevention and Analysis, FDA.

4. Drug Facts and Comparisons, online version, St. Louis, MO (http://factsandcomparisons.com)

Drug Facts and Comparisons is a compendium organized by therapeutic course; contains monographs on prescription and OTC drugs, with charts comparing similar products.

5. AMF Decision Support System [DSS]

DSS is a government database used to track individual submissions and assignments in review divisions.

6. 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.

7. 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.

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

Provides a compilation of approved drug products with therapeutic equivalence evaluations.

9. U.S. Patent and Trademark Office (http://www.uspto.gov)

Provides information regarding patent and trademarks.

10. Clinical Pharmacology Online (www.clinicalpharmacology-ip.com)

Contains full monographs for the most common drugs in clinical use, plus mini monographs covering investigational, less common, combination, nutraceutical and nutritional products. Provides a keyword search engine.

11. 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.

12. Natural Medicines Comprehensive Databases (www.naturaldatabase.com)

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

13. Stat!Ref (www.statref.com)

Contains full-text information from approximately 30 texts. Includes tables and references. Among the database titles are: Handbook of Adverse Drug Interactions, Rudolphs Pediatrics, Basic Clinical Pharmacology and Dictionary of Medical Acronyms Abbreviations.

14. USAN Stems (http://www.ama-assn.org/ama/pub/category/4782.html)

List contains all the recognized USAN stems.

15. Red Book Pharmacy's Fundamental Reference

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

17. Lexi-Comp (www.lexi.com)

A web-based searchable version of the Drug Information Handbook.

16. Medical Abbreviations Book

Contains commonly used medical abbreviations and their definitions.

APPENDICES

Appendix A:

The medication error staff considers the spelling of the name, pronunciation of the name when spoken, and appearance of the name when scripted. DMEPA also compare the spelling of the proposed proprietary name with the proprietary and established name of existing and proposed drug products because similarly spelled names may have greater likelihood to sound similar to one another when spoken or look similar to one another when scripted. The medication error staff also examines the orthographic appearance of the proposed name using a number of different handwriting samples. Handwritten communication of drug names has a long-standing association with drug name confusion. Handwriting can cause similarly *and* dissimilarly spelled drug name pairs to appear very similar to one another and the similar appearance of drug names when scripted has lead to medication errors. The medication error staff apply their expertise gained from root-cause analysis of such medication errors to identify sources of ambiguity within the name that could be introduced when scripting (i.e. "T" may look like "F," lower case 'a' looks like a lower case 'u,' etc), along with other orthographic attributes that determine the overall appearance of the drug name when scripted (see detail in Table 1 below). Additionally, since verbal communication of medication names is common in clinical settings, the medication error staff compares the pronunciation of the proposed proprietary name with the pronunciation of other drug names. If provided, DMEPA will consider the Applicant's intended pronunciation of the proprietary name. However, because the Applicant has little control over how the name will be spoken in practice, DMEPA also considers a variety of pronunciations that could occur in the English language.

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		
	Potential causes of drug name similarity	Attributes examined to identify similar drug names	Potential Effects
Look-alike	Similar spelling	Identical prefix Identical infix Identical suffix Length of the name Overlapping product characteristics	• 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 Upstokes Downstrokes Cross-stokes Dotted letters Ambiguity introduced by scripting letters	• Names may look similar when scripted, and lead to drug name confusion in written communication

		Overlapping product characteristics	
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	• Names may sound similar when pronounced and lead to drug name confusion in verbal communication

Appendix B: FDA Prescription Study Responses

Inpatient Prescription	Voice Prescription	Outpatient Medication Order
Combivent Respimat	Combivent Rispamat	Combivent Respimat
Combivent Respimat	Combivent Respamat	Combivent Respinat
Combivent Respinal	Compement Rispamab	Combivent Respinate
Combivent Respimat	Combimat/Respemat	Combivent Respimist
Combivent Respimat	Combivent rispavent	Combivent Respimat
Combivent Respimat	Combivent Respimed	Combivent Respirant
Combivent Respimat	Combivent Rispimat	Combivent Respimat
	Combivent	
	Combivent Respimat	
	Combivent R	
	Combivent Respimat	
	Combivent Respimat	
	Combivent respimat	

Appendix C: Names that lack convincing orthographic and/or phonetic similarities

Name	Similarity to Combivent Respimat
Atrovent	Look
Perforomist	Look
Respir	Look
Rifamate	Look
Conivaptan	Sound

Appendix D: Proprietary names used only in Foreign Countries

Proprietary Name	Similarity to Combivent Respimat	Country
Respicort	Look	Germany – active ingredient is Budesonide, however, this product is no longer actively marketed. Switzerland – active ingredient is Triamcinolone, however, this product is no longer actively marketed.
Respimex	Look and Sound	Argentina – active ingredient is Ketotifen fumarate.
Respimox	Look	India – active ingredient is Amoxicillin trihydrate/Bromhexine HCL.
Respinal	Look	Philippines – active ingredient is Cephalexin.
Combivent UDV	Look and Sound	Canada – active ingredient is Ipratropium Bromide and Salbutamol.
Berodual Respimat	Look and Sound	Germany – active ingredient is Fenoterol Hydrobromide/Ipratropium Bromide

Appendix E: Products whose proposed proprietary names were discontinued or withdrawn by the Commissioner.

Name	Similarity to Combivent Respimat	Status
Combavia Vitamin	Look	Application withdrawn as of August 7, 1971.
Respital	Look	Application withdrawn as of July 24, 1970.
Resporal	Look	Application withdrawn as of August 27, 1992.
Combipres	Look	Product has been discontinued but is available as Chlorpres.
Respbid	Look	Product no longer actively marketed but is available in generic form.
Respet	Look	Application withdrawn as of September 25, 1973.
Respirol	Look	Product is no longer marketed.

Appendix F: Products with no numerical overlap in strength and dose.

Product name with potential for confusion	Similarity to Combivent Respimat	Strength	Usual Dose
Combivent Respimat (Ipratropium bromide and Albuterol Sulfate)		**20 mcg/100 mcg per actuation**	**Usual dose: One inhalation four times daily, not to exceed 6 inhalations in 24 hours.**
Cernevit-12 (Vitamin A, E, B1, B2, B3, B5, B6, B12, C, biotin FA)	Look	3500 IU, 200 IU, 11.2 IU, 3.51 mg, 4.14 mg, 46 mg, 17.25 mg, 4.53 mg, 5.5 mcg, 125 mg, 60 mcg, 414 mg	Variable, depending on nutrition needs of the patient.
Combigan (Brimonidine tartrate/Timolol)	Look and Sound	0.2%/0.5%	Instill 1 drop to affected eye(s) every 12 hours.
CombiPatch (Estradiol/Norethindrone Acetate)	Look	0.5 mg/0.14 mg, 0.5 mg/0.25 mg	Apply on patch twice weekly during a 28-day cycle, replacing the patch each time.

Combivent Respimat	Both	This tradename is trademarked in multiple countries outside the United States.	-
Combivir (Lamivudine/Zidovudine)	Look and Sound	150 mg/300 mg	1 tablet twice daily.
Respahist (Pseudoephedrine HCl/Brompheniramine Maleate)	Look	60 mg/6 mg	1 to 2 capsules every 12 hours.
Resperal (Dexchlorpheniramine maleate, Dextromethorphan HBr, Phenylephrine HCl, Pyrilamine maleate)	Look	5 mg/5 mg/5 mg/1.25 mg per 5 mL	10 mL by mouth every 4-6 hours.
RespiGam (Respiratory syncytial virus immunoglobulins)	Look	1000 mg/20 mL, 2500 mg/50 mL	750 mg/kg/month.
Respimat	Look and Sound	This is the name of the inhaler.	-
Respi-Tann (Carbetapentane Citrate/Pseudoephedrine HCl)	Look	20 mg/30 mg	10 mL every 12 hours up to 40 mL per day or 2 tablets every 12 hours, up to 8 tablets per day.
Respi-Tann G (Carbetapentane Citrate/Guaifenesin/Tannic Acid)	Look	7.5 mg/200 mg per 5 mL Tannate	10 mL by mouth every 12 hours, not to exceed 40 mL per 24 hours.
RespiVent-D (Methscopolamine nitrate/Pseudoephedrine HCl)	Look	2.5 mg/120 mg	1 tablet by mouth every 12 hours. Do not exceed 2 tablets/day.
Revlimid (Lenalidomide)	Look	5 mg, 10 mg, 15 mg, 25 mg	10 mg to 25 mg by mouth daily.
Risperdal (Risperidone)	Look	0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg, 4 mg	1 mg to 16 mg per day, depending on indication.
(b) (4)	Look and Sound	(b) (4)	

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