

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-348

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**

Date: April, 30, 2009

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Subject: Proprietary Name Review

Drug Name(s): Caldolor (Ibuprofen) Injection 400 mg/4 mL and 800 mg/8 mL vials

Application Type/Number: NDA 22-348

Applicant/Applicant: Cumberland Pharmaceuticals

OSE RCM #: 2009-380

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

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EXECUTIVE SUMMARY

This review is in response to a request from Cumberland Pharmaceuticals dated February 25, 2009, for an assessment of the proposed proprietary name, Caldolor, regarding potential name confusion with other proprietary or established drug names in the usual practice settings. If approved, Caldolor will be the first ibuprofen injection product indicated for pain and fever.

We identified 32 names as having potential orthographic and/or phonetic similarity to Caldolor. Our Failure Mode and Effects Analysis determined that the name similarity between Caldolor and the 32 names was unlikely to result in medication errors related to name confusion. Neither DDMAC or the review division raised any concerns with the proposed name. Thus, the Division of Medication Error Prevention and Analysis (DMEPA) has no objection to the proprietary name, Caldolor, 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 Anesthesia, Analgesia, and Rheumatology Products should notify DMEPA because the proprietary name must be re-reviewed prior to the new approval date.

1 BACKGROUND

1.1 INTRODUCTION

This review is in response to a request from the Applicant, Cumberland Pharmaceuticals dated February 25, 2009 for an assessment of the proposed proprietary name, Caldolor, regarding potential name confusion with other proprietary or established drug names in the usual practice settings. The labels and labeling for this product are reviewed separately in OSE review # 2009-46.

1.2 PRODUCT INFORMATION

Caldolor is the proposed proprietary name for ibuprofen injection to be indicated for the management of mild to severe pain and for the reduction of fever. Caldolor is a 100 mg/ml solution packaged in 400 mg/4 mL and 800 mg/8 mL vials. The dose for pain in adult patients is 800 mg intravenously every six hours. The dose for fever in adult patients is 400 mg intravenously every four to six hours up to 800 mg every 6 hours. The dose of 400 mg and 800 mg must be diluted in 100 mLs and 200 mLs, respectively, of 5 % Dextrose or 0.9 % Sodium Chloride prior to administration.

1.3 REGULATORY HISTORY

The initial proposed name for NDA 22-348, Amelior^{***} was submitted by the Applicant, December 20, 2008. However, the Division of Drug Marketing, Advertising, and Communications (DDMAC) objected to the use of the name "because it overstates and guarantees the efficacy of the product." Thus, Cumberland Pharmaceuticals requested review of an alternate proposed proprietary name, Caldolor.

^{***} Note: This is proprietary and confidential information that should not be released to the public. ^{***}

2 METHODS AND MATERIALS

This section describes the methods and materials used by the Division of Medication Error Prevention and Analysis (DMEPA) when conducting a proprietary name risk assessment (See 2.1 Proprietary Name Risk Assessment). The primary objective for 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 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 CDER.

For the proposed proprietary name, DMEPA staff searched a standard set of databases and information sources to identify names with orthographic and phonetic similarity (See 2.1.1 for details) and held a Center for Drug Evaluation and Research (CDER) Expert Panel discussion to gather professional opinions on the safety of the proposed proprietary name (See 2.1.1.2). DMEPA staff also conducts internal CDER prescription analysis studies. When provided, external prescription analysis studies results are considered and incorporated into the overall risk assessment.

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 2.1.4 for details). 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 FMEA is used 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 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

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.

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

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’ 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 Caldolor, the DMEPA staff also considers the orthographic appearance of the name on lined and unlined orders. Specific attributes taken into consideration include the length of the name (eight letters), and upstrokes (four, capital letter ‘C’, lower case ‘l,’ ‘d,’ and ‘l’). Additionally, several letters in Caldolor may be vulnerable to ambiguity when scripted, (see Appendix B). As a result, the DMEPA staff also considers these alternate appearances when identifying drug names that may look similar to Caldolor.

When searching to identify potential names that may sound similar to Caldolor, the DMEPA staff search for names with similar number of syllables (three), stresses (CAL-do-lor or cal-do-LOR), and placement of vowel and consonant sounds. Additionally, the DMEPA staff considers that pronunciation of parts of the name can vary such as; ‘Cal’ may sound like ‘Ken’. (see Appendix B.) Although the Applicant included the intended pronunciation of the proposed name in the submission, names are often mispronounced and/or spoken with regional accents and dialects, so other potential pronunciations of the name are considered.

The DMEPA staff also considers the product characteristics associated with the proposed drug throughout the identification of similar drug names because the product characteristics of the proposed drug ultimately determine the use of the product in the clinical practice setting. For this review, the following information was provided about the proposed product to the medication error staff: proposed proprietary name (Caldolor), proposed established name

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)

(Ibuprofen), proposed indication of use (pain or fever), strength (400 mg/4 mL and 800 mg/8 mL), solution concentration (100 mg/mL) dose (400 mg or 800 mg), frequency of administration (every four or six hours), route (intravenous), and dosage form (injection in a vial).

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, 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 proprietary name or product based on professional experience with medication errors.

2.1.1.1 Database and Information Sources

The proposed proprietary name 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 the proposed proprietary name using the criteria outlined in Section 2.1.1. A standard description of the databases used in the searches is provided in Section 7. To complement the process, DMEPA used 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 reviewed the USAN stem list to determine if any USAN stems are present within the proprietary name. The individual findings of multiple safety evaluators were then pooled and presented to the CDER 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 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). Potential concerns regarding drug marketing and promotion related to the proposed names are also discussed.

The pooled results of the DMEPA 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 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 a total of 123 (one hundred twenty-three) 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 practitioners.

In order to evaluate the potential for misinterpretation of the proposed proprietary name in handwriting and verbal communication of the name, two inpatient medication orders are written, each consisting of a combination of marketed and unapproved drug products, including the proposed name. Two inpatient orders were utilized as this medication will likely be used in an inpatient setting only. These orders are optically scanned and one prescription is delivered to a random sample of the 123 participating health professionals via e-mail. In addition, a verbal medication order 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 DMEPA.

Figure 1. Caldolor Study (conducted on February 9, 2009)

HANDWRITTEN REQUISITION MEDICATION ORDER	VERBAL PRESCRIPTION
<p data-bbox="293 804 667 835"><u>Inpatient Medication Order #1:</u></p> <p data-bbox="293 846 987 919"><i>Caldolor 800mg IV q 6 hrs</i></p>	<p data-bbox="1078 804 1284 835">Caldolor 800 mg</p> <p data-bbox="1040 852 1321 940">Infuse 800 mg intravenously every six hours.</p>
<p data-bbox="293 945 667 976"><u>Inpatient Medication Order #2:</u></p> <p data-bbox="293 1014 987 1108"><i>Caldolor 800mg infuse 800mg intravenously every 6 hours</i></p>	

2.1.3 Comments from the OND review Division

DMEPA requests the regulatory division in the Office of New Drugs responsible for the application for their comments or concerns with the proposed proprietary name and 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. Any comments or concerns are addressed in the safety evaluator’s assessment.

The 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 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, the Safety Evaluator Risk Assessment applies his/her individual expertise gained from evaluating medication errors reported to FDA to conduct 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.⁶ 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 as a result of the 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 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 Caldolor 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 Caldolor 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 possess similarity that would cause confusion at any point in the medication use system, then 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 not ultimately 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; for example, 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:

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

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, 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)].
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 (United States Adopted Names) stem, particularly in a manner that is contradictory to the USAN Council's definition.
5. 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.

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 criteria are met, then DMEPA will not object to the use of the proprietary name. If any of these criteria are met, then DMEPA will object to the use of the proposed 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 Institute of Medicine (IOM), World Health Organization (WHO), Joint Commission on Accreditation of Hospitals (JCOAH), and the Institute for Safe Medication Practices (ISMP), who 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 and other post-approval efforts are low-leverage strategies that have proven to have limited effectiveness at alleviating 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 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).

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. 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.

3 RESULTS

3.1 PROPRIETARY NAME RISK ASSESSMENT

3.1.1 Database and Information Sources

The searches yielded a total of 31 names as having some similarity to the name Caldolor.

Twenty-three of the names were thought to look like Caldolor. These include Aldoclor-150, Aldoclor- 50, Aldoril, (b) (4) Calafol, Calafol-Rx, Calciferol, (b) (4) Calcimar, Calcitriol, Caldor-D, Caldecort, Caldon, Caldoxon, Calomist, C (b) (4) Cancidas, Carteolol, Carvedilol, Clolar, (b) (4), Endolor, and Nadolol. One name, (b) (4)*, was thought to sound like Caldolor. The remaining seven names were thought to look and sound similar to Caldolor: Aldolor, Calcidol, Calderol, Caldoral, Carnitor, Paldolor, and (b) (4).

Additionally, DMEPA staff did not identify any United States Adopted Names (USAN) stems in the proposed proprietary name, as of April 29, 2009.

3.1.2 Expert Panel Discussion

The Expert Panel reviewed the pool of names identified by DMEPA staff (See Section 3.1.1 above) and noted no additional names thought to have orthographic or phonetic similarity to Cambia.

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 26 practitioners responded but none of the responses overlapped with any existing or proposed drug names. Seven of the participants interpreted the name correctly as "Caldolor,"

*** Note: This is proprietary and confidential information that should not be released to the public.***

with correct interpretation occurring in the inpatient order #1 written studies (n=1), in the inpatient order #2 written studies (n=5), and in the verbal studies (n=1). The remainder of the written responses misinterpreted the drug name. In the verbal studies, the remaining responses were misspelled phonetic variations of the proposed name, Caldolor. See Appendix B for the complete listing of interpretations from the verbal and written prescription studies.

3.1.4 Comments from the Division of Analgesia, Anesthesia and Rheumatology Products

In response to the OSE March 4, 2009 e-mail, the Division of Anesthesia, Analgesia, and Rheumatology Products did not forward any comments and or concerns on the proposed proprietary name at the initial phase of the name review.

DMEPA notified the Division of Anesthesia, Analgesia, and Rheumatology Products via e-mail that we had no objections to the proposed proprietary name; Caldolor, on April 10, 2009. Per e-mail correspondence from the Division of Anesthesia, Analgesia, and Rheumatology Products on April 13, 2009, they indicated they concur with our assessment of the proposed proprietary name, Caldolor.

3.1.5 Safety Evaluator Risk Assessment

Independent searches by the primary Safety Evaluator resulted in two additional names which were thought to look or sound similar to Caldolor and represent a potential source of drug name confusion.

The name, Aldactone, was identified to have look-alike similarities. The name, Ketalar, was identified as to have sound-alike similarities. Additionally, we note that attempts to identify the drug names, Cadoral, were unsuccessful. We assume that the name was misspelled during the search process (i.e. Cadoral for Caldoral identified in Section 3.1.1 above). Thus, we evaluated Caldoral.

4 DISCUSSION

Consideration was given to the comments of both DDMAC and the review division. Our searches identified thirty-two names which were evaluated for their potential similarity to the proposed name, Caldolor.

Failure mode and effect analysis (FMEA) was then applied to determine if the potential name could potentially be confused with any of the thirty-two names and lead to medication errors. This analysis determined that the name similarity between Caldolor was unlikely to result in medication errors with any of the thirty-two products for the reasons presented in Appendices D through H.

5 CONCLUSIONS AND RECOMMENDATIONS

The Proprietary Name Risk Assessment findings indicate that the proposed name, Caldolor, is not vulnerable to name confusion that could lead to medication errors. Neither DDMAC or the review division objected to the proposed name. Thus the Division of Medication Error Prevention and Analysis (DMEPA) has no objection to the proprietary name, Caldolor, for this product at this time.

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 Anesthesia, Analgesia, and Rheumatology

Products should notify DMEPA because the proprietary name must be re-reviewed prior to the new approval date.

5.1 COMMENTS TO THE DIVISION

We note the PDUFA date for this application is June 11, 2009; therefore, we consider this a final review. If the approval is extended beyond 90 days from the signature date of this review, DMEPA must re-review the name, Caldolor, 90 days prior to its anticipated approval date.

Please copy DMEPA on any communication to the Applicant with regard to this review. If you have further questions or need clarifications, please contact Chris Wheeler, project manager, at 301-796-0151.

5.2 COMMENTS TO THE APPLICANT

5.2.1 Proprietary Name

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

6 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. ***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:

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 compares 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 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 medication error 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), along with other orthographic attributes that determine the overall appearance of the drug name when scripted (see Table 1 below for details). In addition, the medication error 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.

Table 1. Criteria used to identify drug names that look- or sound-similar to a proposed proprietary name.

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

Appendix B: Letters with possible orthographic or phonetic misinterpretation

Letters in Name, Caldolor	Scripted may appear as	Spoken may be interpreted as
Capital 'C'	A or L	'k' or 'q'
lower case 'c'	a, e, i, or l	'k' or 'q'
lower case 'a'	c, 'ci,' 'ce.' o, u, or x	any vowel
lower case 'l'	b, c, e, or i	'n'
lower case 'd'	'cl' or 'el'	't'
lower case 'o'	a, u, or v	any vowel
lower case 'r'	n, s, t, u, v, or x	

Appendix C: CDER Prescription Study Responses.

Inpatient Medication Order	Outpatient Medication Order	Voice Prescription
Caldolar	Caldolor	Caldalor
Caldalar	Caldolor	Caldalore
Caldolar	Caldolor	Cavalore
Caldolar	Caldalor	Caldelor
Caldolar	Caldolor	Calomore
Caldolor	Caldolor	Caldelor
	Caldolar	Caldelor
		Caldolor
		Caldalar
		Caldalar

Appendix D: Products marketed in Foreign Countries.

Name	Similarity to Caldolor	Country
Caldar-D	Look	Chile
Caldoxon	Look	Thailand
Aldolor	Look and Sound	Israel
(b) (4)	Look and Sound	Columbia
(b) (4)	Look and Sound	Norway

Appendix E: Products not identified as marketed drug products.

Name	What it is or where name found
Caldon	Tradename for chemical-2,4-Dinitro-6-sec-butylphenol
Paldolor	Found in US Trademark office database as drug containing ointment, but no listing in any other of our usually monitored databases.

Appendix F: Products discontinued from the market with no generic equivalent.

Name	Similarity to Caldolor	Year discontinued/withdrawn from the market
Aldoclor-150	Look	2004
Aldoclor-50	Look	2004
Calderol	Look and Sound	2002
Calcimar	Look	2007
(b) (4)***	Look	Withdrawn by Commissioner 1974 (unapproved NDA)

*** Note: This is proprietary and confidential information that should not be released to the public.***

Appendix G: Products with no overlap in strength and dose.

Product name with potential for confusion	Similarity to Proposed Proprietary Name	Strength	Usual Dose (if applicable)
Caldolor (Ibuprofen) Injection		400 mg/4 mL or 800 mg/8 mL (100 mg/mL)	400 mg intravenously every four hours, as needed or 800 mg every six hours, as needed.
Aldoril (Methyldopa or Methyldopate HCl) Trade name product discontinued but generic equivalents available.	Look	250 mg and 500 mg tablets 250 mg/5 mL vial	One tablet (250 mg or 500 mg) by mouth every six hours. 250 mg or 500 mg intravenously every six hours.
Calafol or Calafol Rx (vitamin supplement)	Look	no strength	One tablet by mouth twice daily.
Calcidol (ergocalciferol)	Look and Sound	8288 international units/mL	Two drops (415 units) by mouth daily.
Calcitriol (established name for Rocaltrol and Calcijex)	Look	0.25 mcg and 0.5 mcg capsules and 1 mcg/mL oral solution 1 mcg/mL injection	One capsule or 0.25 mL (0.25 mcg) by mouth daily. One or two mLs (1 to 2 mcg) three times weekly intravenous push following hemodialysis.
Caldecort (Hydrocortisone)	Look	1% cream	Apply topically three to four times daily.
Calomist (cyanocobalamin)	Look	25 mcg per actuation	One spray (25 mcg) per nostril daily.
Caltrate (Calcium Carbonate) family of products with Vitamin D and some with others minerals such as Magnesium	Look	600 mg of calcium (as carbonate) tablets	One tablet (600 mg) by mouth twice daily with food.
Cancidas (Caspofungin)	Look	50 mg or 70 mg vials for injection	70 mg intravenously on day one, then 50 mg intravenously daily.

Carnitor (Levocarnitine)	Look and Sound	330 mg tablet 1 g/10 ml oral solution 1 g/5 mL ampule	Three tablets by mouth three times daily. Ten mLs (1 g) by mouth three times daily. or 50-100 mg/kg/day divided into three doses (pediatric) 10-20 mg/kg intravenously with each dialysis.
Carteolol (established name for Ocupress)	Look	1 % ophthalmic solution	One drop into affected eye twice daily.
Clolar (Clofarabine)	Look	20 mg/20 mL	52 mg/m ² intravenously daily for five days.
██████████	(b) (4)	██████████	██████████
Endolor (Acetaminophen, Butalbital, and Caffeine)	Look	325 mg/50 mg/ 40 mg tablet	One to two tablets every four hours as needed, maximum of six tablets in 24 hours.
Kalbitor*** (ecallantide)	Sound	10 mg	Three vials (30 mg) subcutaneously one time.

Appendix H: FMEA Table of products with similar strengths or doses.

Caldolor (Ibuprofen) Injection	400 mg/4 mL or 800 mg/8 mL (100 mg/mL)	400 mg intravenously every four hours, as needed, or 800 mg every six hours, as needed.
Failure Mode: Name confusion	Causes	Effects
Aldactone (Spironolactone) 25 mg, 50 mg and 100 mg tablets	Orthographic similarity: 'A' may appear as 'C' when scripted; both names include the letters 'ld' together as upstrokes; 'a' may appear as 'o' when scripted; both names have an upstroke in a similar position in names ('t' vs. 'l'); and the letters 'on' may appear as 'or' when	Orthographic differences between the names and differences in product characteristics minimize the potential for medication errors in usual practice settings. <i>Rationale:</i> Orthographic differences stem from the fact an 'a' separates the 'C' and 'l' in Caldolor while no letter separates the 'A' from the 'l' in Aldactone. In addition, Aldactone includes a 'c' separating the 'a' and upstroke of the 't' and an additional letter 'e' at the end on the name.

*** Note: This is proprietary and confidential information that should not be released to the public.***

	<p>scripted.</p> <p>Same numerical strength (100 mg vs. 100 mg/mL)</p> <p>Overlapping achievable dose (400 mg)</p>	<p>Aldactone is an oral tablet taken daily as a routine medication for edema or hypertension. Dose is usually 25 mg to 100 mg</p> <p>Caldolor is administered as an intravenous infusion at doses of 400 mg to 800 mg every four to six hours as needed to control pain or fever.</p> <p>Caldolor is an injectable solution available in vials.</p>
<p>Calciferol (ergocalciferol) 8000 USP units/mL oral drops 60 ml bottle</p>	<p>Orthographic similarity: Both names begin with the same three letters 'Cal;' 'ci' may appear similar to 'o' when scripted; and both names have letter groupings with similar appearances when scripted ('fer' vs. 'lor').</p> <p>Numerically similar strengths (8000 USP units/mL vs. 800 mg/8 mL)</p> <p>Numerically overlapping doses (400 USP units vs. 400 mg)</p>	<p>Orthographic differences between the names and differences in product characteristics minimize the potential for medication errors in usual practice settings.</p> <p><i>Rationale:</i></p> <p>Orthographic differences stem from the fact Calciferol lacks an upstroke following the first 'l' and has two additional letters 'ol' following the 'r' at the end of the name providing added length and an additional upstroke. Caldolor includes the letter 'd' following the first 'l' which does provide a consecutive upstroke in the name.</p> <p>Calciferol is a nutritional supplement taken orally once daily.</p> <p>Caldolor is administered as an intravenous infusion every four to six hours as needed to control pain or fever.</p>
<p>Carvedilol (established name for Coreg and as phosphate for Coreg CR) Coreg: 3.125 mg, 6.25 mg, 12.5 mg, and 25 mg tablets Coreg CR: 10 mg, 20 mg, 40 mg, and 80 mg extended-release capsules</p>	<p>Orthographic similarity: both names begin with 'Ca' and both names have a similar grouping at the end of the name ('edilol' vs. 'ldolor') when scripted.</p> <p>Numerically similar strength: 100 mg/ml vs. 10 mg.</p> <p>Numerically similar doses: 400 mg and 800 mg vs. 40 mg and 80 mg.</p>	<p>Orthographic differences between the names and differences in product characteristics minimize the potential for medication errors in usual practice settings.</p> <p><i>Rationale:</i></p> <p>Orthographic differences in the names stem from the fact Carvedilol includes the letter grouping 'rv' between 'Ca' and 'ed' providing added length and an upstroke at the end of the name provided by the letter 'l.'</p> <p>Coreg CR is an oral capsule taken daily as a routine treatment of heart failure or hypertension and likely ordered by the proprietary name (Coreg CR) to minimize confusion with the immediate release tablets.</p> <p>Caldolor is administered as an intravenous infusion at doses of 400 mg to 800 mg every four to six hours as needed to control pain or fever.</p> <p>Caldolor is an injectable solution available in vials.</p>

<p>Ketalar (Ketamine HCl) 200 mg/ 20 mL (10 mg/mL), 500 mg/10 mL (50 mg/mL) and 500 mg/5 mL (100 mg/mL) vials</p>	<p>Phonetic similarity: Both names have three syllables and begin with the 'Kah-' sound; the second syllable in each name begins with similar sounding letters ('t' vs. 'd'); and the third syllable can sound almost identical ('lar' vs. 'lor').</p> <p>Same product concentration: 100 mg/mL.</p> <p>Both products are injectable solutions packaged in a vial and may be diluted in a bag of fluids prior to administration.</p>	<p>Phonetic differences between the names and differences in product characteristics minimize the potential for medication errors in usual practice settings.</p> <p><i>Rationale:</i></p> <p>Phonetic differences stem from the vowel sound in the first syllable ('ee' vs. 'ah') and the added 'l' after the 'ah' in Caldolor.</p> <p>Ketalar is used specifically with anesthesia for induction and maintenance.</p> <p>Although the vial concentrations may overlap, both products are available in multiple strengths which are likely specified in a computerized line listing.</p>
<p>Nadolol (established name for Corgard) 10 mg, 20 mg and 40 mg tablets</p>	<p>Orthographic similarity: the second letter in both names is the same 'a' and both names contain the same four letter grouping ('dolo').</p> <p>Numerically similar strength (10 mg vs. 100 mg/mL).</p> <p>Numerically similar dose (40 mg vs. 400 mg).</p>	<p>Orthographic differences between the names and differences in product characteristics minimize the potential for medication errors in usual practice settings.</p> <p><i>Rationale:</i></p> <p>Orthographic differences in the names stem from the fact Nadolol begins with 'N' and ends with an upstroke provided by 'l.' In addition, Caldolor includes an 'l' as the third letter separating 'a' and 'd.'</p> <p>Nadolol is an oral tablet taken daily as a routine medication for angina or hypertension.</p> <p>Caldolor is administered as an intravenous infusion at doses of 400 mg to 800 mg every four to six hours as needed to control pain or fever.</p> <p>Caldolor is an injectable solution available in vials.</p>

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