

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

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PROPRIETARY NAME REVIEW(S)

**Department of Health and Human Services
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Subject: Proprietary Name Review

Drug Name(s): (Roflumilast) Tablets, 500 mcg

Applicant: Forest Research Institute, Inc.

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CONTENTS

EXECUTIVE SUMMARY	3
1 BACKGROUND.....	3
1.1 Introduction.....	3
1.2 Product Information	3
2 METHODS AND MATERIALS	3
2.1 Search Criteria.....	3
2.2 Prescription Analysis Studies.....	4
2.3 External Proprietary Name Risk Assessment	4
3 RESULTS.....	4
3.1 Data base and Information Sources.....	5
3.2 Expert Panel Discussion.....	5
3.3 Prescription Analysis Studies.....	5
3.4 External Study.....	5
3.5 Safety Evaluator Risk Assessment.....	5
3.6 Comments from the Division of Pulmonary, Allergy and Rheumatology Products.....	6
4 DISCUSSION	6
4.1 Promotional Assessment	6
4.2 Safety Assessment.....	6
5 CONCLUSIONS AND RECOMMENDATIONS	6
5.1 Comments to the Applicant.....	7
6 REFERENCES	8
APPENDICES	9

EXECUTIVE SUMMARY

This review summarizes DMEPA's evaluation of Daliresp as the proposed proprietary name for Roflumilast Tablets. Our evaluation did not identify concerns that would render the name unacceptable based on the product characteristics and safety profile known at the time of this review. Thus, DMEPA finds the proposed proprietary name Daliresp acceptable for this product. The proposed proprietary name must be re-reviewed 90 days before approval of the NDA. DMEPA will notify the Applicant of these findings via letter

Additionally, 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.

1 BACKGROUND

1.1 INTRODUCTION

This review responds to a request from Forest Laboratories dated February 25, 2011 for a promotional and safety assessment of the proposed proprietary name, Daliresp.

1.2 PRODUCT INFORMATION

Daliresp (Roflumilast) is a phosphodiesterase-4 (PDE-4) inhibitor, a non-steroid anti-inflammatory agent, indicated for maintenance treatment of severe Chronic Obstructive Pulmonary Disease (COPD) associated with chronic bronchitis. The usual recommended dose of Daliresp (Roflumilast) is one 500 microgram tablet taken by mouth once daily with food. Daliresp (Roflumilast) is not recommended for patients with hepatic impairment. Daliresp (Roflumilast) will be available as a yellow 500 microgram tablet, packaged in bottles containing 30 or 90 tablets (b) (4)

2 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 proprietary name risk assessment for all proprietary names. Sections 2.1 and 2.2 identify specific information associated with the methodology for the proposed proprietary name, Daliresp. Section 2.3 identifies specific information associated with the methodology for assessment of the proposed labels and labeling.

2.1 SEARCH CRITERIA

For this review, particular consideration was given to drug names beginning with the letter 'D' 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.^{1,2}

¹ Institute for Safe Medication Practices. Confused Drug name List (1996-2006). Available at <http://www.ismp.org/Tools/confuseddrugnames.pdf>

To identify drug names that may look similar to Daliresp, the DMEPA safety evaluators 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), upstrokes (two, capital letter ‘D’, and lower case ‘l’), down strokes (one, lower case ‘p’), cross strokes (none), and dotted letters (one, lower case ‘i’). Additionally, several letters in Daliresp 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 Daliresp.

When searching to identify potential names that may sound similar to Daliresp, the DMEPA staff search for names with similar number of syllables (three), stresses (da-li-resp), and placement of vowel and consonant sounds. (See Appendix B). The Applicant’s intended pronunciation (da'-li-resp) was also taken into consideration, as it was included in the Proprietary Name Review Request. Moreover, names are often mispronounced and/or spoken with regional accents and dialects, so other potential pronunciations of the name are considered.

2.2 PRESCRIPTION ANALYSIS STUDIES

In order to evaluate the potential for misinterpretation of the proposed proprietary name in handwriting and verbal communication of the name, the following inpatient medication order, outpatient and verbal prescription was communicated during the FDA prescription studies. (See Appendix C for samples and results).

2.3 EXTERNAL PROPRIETARY NAME RISK ASSESSMENT

For this product, the Applicant submitted an external evaluation of the proposed proprietary name. The Division of Medication Error Prevention and Analysis conducts an independent analysis and evaluation of the data provided, and responds to the overall findings of the assessment. When the external proprietary name risk assessment identifies potentially confusing names that were not captured in DMEPA’s database searches or in the Expert Panel Discussion, these names are included in the Safety Evaluator’s Risk Assessment and analyzed independently by the Safety Evaluator to determine if the potentially confusing name could lead to medication errors in usual practice settings. After the Safety Evaluator has determined the overall risk associated with proposed name, the Safety Evaluator compares the findings of their overall risk assessment with the findings of the proprietary name risk assessment submitted by the Applicant. The Safety Evaluator then determines whether the Division’s risk assessment concurs or differs with the findings. When the proprietary name risk assessments differ, the Division of Medication Error Prevention and Analysis provides a detailed explanation of these differences.

3 RESULTS

The following sections describe the findings from our database searches, expert panel discussion, prescription analysis studies and safety evaluator risk assessment.

² Kondrack, G and Dorr, B. ³ National Coordinating Council for Medication Error Reporting and Prevention. <http://www.nccmerp.org/aboutMedErrors.html>. Last accessed 10/11/2007.

3.1 DATA BASE AND INFORMATION SOURCES

The DMEPA safety evaluator searches yielded a total of 11 names as having some similarity to the name Daliresp.

Eight of the names were thought to look like Daliresp. These include: Aranesp, Dralserp, Salagen, Dermatop, Duraprep, Diabinese, Dallery, and (b) (4)***. Two names were thought to look and sound similar to Daliresp: Daliresp *** and Dolorex. One name was thought to sound like Daliresp: Valtrex.

Additionally, DMEPA staff did not identify any United States Adopted Names (USAN) stems in the proposed proprietary name, as of February 17, 2011.

3.2 EXPERT PANEL DISCUSSION

The Expert Panel reviewed the pool of names identified by DMEPA staff (See Section 3.1 above) and noted no additional names thought to have orthographic or phonetic similarity to Daliresp.

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

3.3 PRESCRIPTION ANALYSIS STUDIES

A total of 27 practitioners responded to the prescription analyses studies. In the written prescription study, thirteen of the participants interpreted the scripted name sample correctly only in the outpatient study. Most of the written responses misinterpreted the letter 'D' as the letter 'cl' in the inpatient study. Incorrect written interpretations did not overlap with existing drug product names. In the verbal studies, all the participants misinterpreted the name incorrectly. See Appendix C for the complete listing of interpretations from the verbal and written prescription studies.

3.4 EXTERNAL STUDY

The proprietary name risk assessment submitted by Forest found the proposed proprietary name acceptable. In the proposed name risk assessment submitted by the Applicant, the (b) (4) identified and evaluated a total of 12 drug names including: Allerest, Aranesp, Dalmane, Delestrogen, Darunavir, Dermatest, Dolobid, Dolorex, Duranest, Janumet, Tolerex, and Valtrex. Three of these names (Aranesp, Dolorex, and Valtrex) were also identified by DMEPA during the database searches. The remaining nine names were added to the safety evaluator's assessment.

3.5 SAFETY EVALUATOR SEARCHES

Independent searches by the primary Safety Evaluator did not identify any additional names which were thought to look or sound similar to Daliresp and represent a potential source of drug name confusion.

One name "Daliresp" was not evaluated further since it was identified on the U.S. Patent and Trademark Office website registered to the Applicant likely for this product. Thus, we evaluated a total of 19 names: 9 identified by (b) (4) 10 identified in section 3.1 above.

3.6 COMMENTS FROM THE DIVISION OF PULMONARY, ALLERGY AND RHEUMATOLOGY (DPARP)

3.6.1 Initial Phase of Review

In response to the OSE, February 17, 2011 e-mail, DPARP did not forward any concerns on the proposed name at the initial phase of the name review.

3.6.2 Midpoint of Review

DMEPA notified the DPARP via e-mail that we had no concerns with the proposed proprietary name, Daliresp, on February 24, 2011. Per e-mail correspondence from the DPARP on February 24, 2011, they indicated the Division had no other issues with the proposed proprietary name, Daliresp and had no additional comments.

4 DISCUSSION

This proposed name was evaluated from a safety and promotional perspective based on the product characteristics provided by the Applicant. We sought input from pertinent disciplines involved with the review of this application and considered their comments accordingly.

4.1 PROMOTIONAL ASSESSMENT

DDMAC had no concerns regarding the proposed name from a promotional perspective, and did not offer any additional comments relating to the proposed name. DMEPA, and DDOP concurred with the findings of DDMAC's promotional assessment of the proposed name.

4.2 SAFETY ASSESSMENT

DMEPA evaluated 19 names for their potential similarity to the proposed name, Daliresp. We did not identify any other aspects of the name that would be considered as a potential source for error.

Eight of the nineteen potentially similar names did not undergo failure mode and effect analysis (FMEA) for the following reasons: Names lacking significant orthographic similarity, supplement not identified as drug and not dispensed pursuant to a prescription, discontinued products with no available generics, proposed proprietary names withdrawn by the Applicant (see Appendices D-G).

Failure mode and effects analysis (FMEA) was applied to determine if the proposed proprietary name could potentially be confused with the remaining 11 names and lead to medication errors. This analysis determined that the name similarity between Daliresp and all of the identified names was unlikely to result in medication error for the reasons presented in Appendices H and I.

5 CONCLUSIONS AND RECOMMENDATIONS

The Proprietary Name Risk Assessment findings indicate that the proposed name, Daliresp, is not vulnerable to name confusion that could lead to medication errors, nor is it considered promotional. Thus, the Division of Medication Error Prevention and

Analysis (DMEPA) has no objection to the proprietary name, Daliresp, for this product at this time.

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 Applicant will be notified of this determination via letter from DMEPA.

5.1 COMMENTS TO THE APPLICANT

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

The proposed proprietary name must be re-reviewed 90 days before 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 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.

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

DARRTS is a government database used to organize Applicant and Applicant 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. 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/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 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.³

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. DMEPA staff also conducts internal CDER prescription analysis studies. When provided, DMEPA considers external prescription analysis study results and incorporate 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. 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.⁴ 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 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.⁵ 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 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

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

⁵ Institute of Medicine. Preventing Medication Errors. The National Academies Press: Washington DC. 2006.

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.

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	<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 Down strokes Cross-strokes Dotted letters Ambiguity introduced by scripting letters Overlapping product characteristics	<ul style="list-style-type: none"> Names may look similar when scripted, and lead to drug name confusion in written communication
Sound-alike	Phonetic similarity	Identical prefix Identical infix Identical suffix Number of syllables Stresses Placement of vowel sounds Placement of consonant sounds Overlapping product characteristics	<ul style="list-style-type: none"> Names may sound similar when pronounced and lead to drug name confusion in verbal communication

Lastly, 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 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 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. 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 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 the 123 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 DMEPA.

4. Comments from the OND review Division or Generic drugs

DMEPA requests the Office of New Drugs (OND) or Office of Generic Drugs (OGD) Regulatory Division 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. The primary Safety Evaluator addresses any comments or concerns in the safety evaluator's assessment.

The OND or 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 concur/not concur with DMEPA's final decision.

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, 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.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 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 possess similarity that would cause confusion at any point in the medication use system, thus the name is eliminated from further review.

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

⁶ 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), and demonstrates that medication errors are likely to result from the drug name confusion under the conditions of usual clinical practice.
- d. The proposed proprietary name contains an USAN (United States Adopted Names) stem.
- e. DMEPA identifies a potential source of medication error within the proposed proprietary name. For example, the proprietary name may be misleading or, inadvertently, introduce ambiguity and confusion that leads to errors. Such errors may not necessarily involve confusion between the proposed drug and another drug product.

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), 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 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).

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.

Appendix B: Letters with possible orthographic or phonetic misinterpretation

Letters in Name, Daliresp	Scripted may appear as	Spoken may be interpreted as
Upper case 'D'	B,cl, A	T, b
Lower case 'a'	Any vowel	Any vowel
Lower case 'l'	B,t	
Lower case 'i'	Any vowel	Any vowel
Lower case 'r'	N,s,i	
Lower case 'e'	Any vowel	Any vowel
Lower case 's'	N,r.	
Lower case 'p'	Q, y	D,b

Appendix C: FDA Prescription Study for Daliresp

Figure 1. Daliresp Study Samples (conducted on February 14, 2010)

HANDWRITTEN REQUISITION MEDICATION ORDER	VERBAL PRESCRIPTION
<p>Medication Order</p> <p><i>daliresp + tab orally daily</i></p> <hr/> <p>Outpatient Rx</p> <p><i>daliresp</i></p> <p><i>1/1 tab po Qday</i></p> <p><i># 30</i></p> <hr/>	<p>Daliresp 1 tablet po daily #30</p>

Table 1: Responses to Prescription Study

Outpatient Prescription	Inpatient Medication Order	Voice Prescription
Daliresp	Clabresp	Dalurest
Dabresp	Clatresp	Dalleres
Daliresp	Clariresp	Dalurest
Daliresp	Clariresp	Dalerus
Dalirsp	Clariresp	Dalurise
Daliresp		Dalarath
Daliresp		
Dabresp		
Daliresp		

Appendix D: Proprietary names that lack convincing orthographic and/or phonetic similarities

Proprietary Name	Similarity to Daliresp	Proprietary Name	Similarity to Daliresp
Delestrogen	Look	Darunavir	Look
Dolobid	Look	Janumet	Look
Valtrex	Look		

Appendix E: OTC, Herbal Product, or Supplement not identified as drug and not dispensed pursuant to a prescription.

Proprietary Name	Similarity to Daliresp	Reason
Tolerex	Look	Lactose free elemental formula

Appendix F: Discontinued products with no available generics

Proprietary Name	Similarity to Daliresp	Reason
Dralserp (Hydralazine and Resepine) Tablets	Look	Discontinued products with no available generics

Appendix G: Proposed proprietary names

Proprietary Name	Similarity to Daliresp	Status
(b) (4)**	Look	Name was withdrawn by the Applicant. The new proposed name for this product is Daliresp which is being evaluated in this review.

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

Appendix H: Products with orthographic, phonetic and/or multiple differentiating product characteristics minimize the risk for medication errors

Product name with potential for confusion	Similarity to Daliresp	Strength	Usual Dosage and Administration	Name confusion is prevented by the combination of stated product characteristics, orthographic, and/or phonetic differences as described.
Daliresp (Roflumilast) Tablets	N/A	Single strength 500 mcg	1 tablet daily	N/A
Allerest (Acetaminophen-pseudoephedrine - chlorpheniramine maleate) Caplets and Tablets	Look alike	Caplets: 325 mg-30 mg-2 mg Tablets 2 mg- 30 mg	Oral caplets: 1 caplet 4-6 times daily Oral tablets: One tablets 2 times daily	Orthographic differences in the names, in conjunction with differences in product characteristics, minimize the likelihood of medication error in the usual practice setting. <u>Orthographic:</u> <i>Allerest has four upstrokes in the name vs. two in Daliresp.</i> <i>Daliresp has a downstroke 'p' at the end of the name which is absent in Allerest</i> <u>Frequency:</u> <i>Once daily vs. 2 times daily or 4-6 times daily</i> <u>Regulatory Status:</u> <i>Prescription vs. over the counter</i>
Aranesp (Darbepoetin Alfa) Injection Solution	Look alike	25 mcg/mL 40 mcg/mL 60 mcg/mL 100 mcg/mL 150 mcg/0.75 mL 200 mcg/mL 300 mcg/mL	Individualize dosing to achieve and maintain hemoglobin levels to a target range of 10-12 g/dL. Usual dose ranges from 25 mcg once weekly to 300 mcg weekly or every 2 weeks or 0.45mcg/kg per dose, 2.25- 4.5mcg/kg per dose	Orthographic differences in the names, in conjunction with differences in product characteristics, minimize the likelihood of medication error in the usual practice setting. <u>Orthographic:</u> <i>Daliresp has an upstroke 'l' in the name which is absent in Aranesp.</i> <u>Dosage form:</u> <i>Tablet vs. injection solution</i> <u>Route of Administration:</u> <i>Oral vs. subcutaneous or intravenous injection</i> <u>Frequency:</u> <i>Once daily vs. once weekly or every 2 weeks</i>

Product name with potential for confusion	Similarity to Daliresp	Strength	Usual Dosage and Administration	Name confusion is prevented by the combination of stated product characteristics, orthographic, and/or phonetic differences as described.
Daliresp (Roflumilast) Tablets	N/A	Single strength 500 mcg	1 tablet daily	N/A
Dermatest (Hydrocortisone) Topical Lotion	Look alike	Single strength 1%	One application 2 to 4 times daily	<p>Orthographic differences in the names, in conjunction with differences in product characteristics, minimize the likelihood of medication error in the usual practice setting.</p> <p><u>Orthographic:</u> <i>The position of the second upstroke is different in the two names. Daliresp has a downstroke at the end of the name vs. Dermatest has an upstroke in that position.</i></p> <p><u>Dosage form:</u> <i>Tablet vs. topical lotion</i></p> <p><u>Route of Administration:</u> <i>Oral vs. topical</i></p> <p><u>Dose:</u> <i>One tablet or 500 mcg vs. one application</i></p> <p><u>Frequency:</u> <i>Once daily vs. two to four times daily</i></p>
Dolorex (Hydrocodone and Acetaminophen)	Look alike	5 mg/500 mg	One to two tablets every 4 to 6 hours as needed	<p>Orthographic differences in the names, in conjunction with differences in product characteristics, minimize the likelihood of medication error in the usual practice setting.</p> <p><u>Orthographic:</u> <i>Daliresp has a downstroke at the end of the name which is absent in dolorex.</i></p> <p><u>Frequency:</u> <i>Once daily vs. every 4 to 6 hours as needed</i></p> <p><u>Use data:</u> <i>Preliminary usage data indicates that the product is not prescribed under the name Dolorex.</i></p>

Product name with potential for confusion	Similarity to Daliresp	Strength	Usual Dosage and Administration	Name confusion is prevented by the combination of stated product characteristics, orthographic, and/or phonetic differences as described.
Daliresp (Roflumilast) Tablets	N/A	Single strength 500 mcg	1 tablet daily	N/A
Duranest (Etidocaine) Injection Solution	Look Alike	10 mg/mL	Dosage varies on patient weight and indication (usually 8 mg/kg). It is given intramuscularly or subcutaneously once prior to procedure	<p>Orthographic differences in the names, in conjunction with differences in product characteristics, minimize the likelihood of medication error in the usual practice setting.</p> <p><u>Orthographic:</u> <i>Daliresp has a downstroke at the end of the name vs. Dermatest has an upstroke in that position.</i></p> <p><u>Route of Administration:</u> <i>Oral vs. intramuscularly or subcutaneously</i></p> <p><u>Dosage form:</u> <i>Tablet vs. injection solution</i></p> <p><u>Frequency:</u> <i>Once daily vs. once prior to procedure</i></p>
Salagen (Pilocarpine) Tablets	Look alike	5 mg 7.5 mg	5 mg to 10 mg three to four times daily	<p>Orthographic differences in the names, in conjunction with differences in product characteristics, minimize the likelihood of medication error in the usual practice setting.</p> <p><u>Orthographic:</u> <i>The position of the downstroke is different in the two names.</i></p> <p><u>Frequency:</u> <i>Once daily vs. three to four times daily</i></p>
Dermatop (Prednicarbate) topical Cream and Ointment	Look alike	0.1%	One application two times daily	<p>Orthographic differences in the names, in conjunction with differences in product characteristics, minimize the likelihood of medication error in the usual practice setting.</p> <p><u>Orthographic:</u> <i>The position of the second upstroke is different in the two names.</i></p> <p><u>Dose:</u> <i>One tablet or 500 mcg vs. one application</i></p> <p><u>Dosage form:</u> <i>Tablet vs. topical cream and ointment</i></p> <p><u>Route of Administration:</u> <i>Oral vs. topical</i></p>

Product name with potential for confusion	Similarity to Daliresp	Strength	Usual Dosage and Administration	Name confusion is prevented by the combination of stated product characteristics, orthographic, and/or phonetic differences as described.
Daliresp (Roflumilast) Tablets	N/A	Single strength 500 mcg	1 tablet daily	N/A
Duraprep (Iodine Povacrylex and Isopropyl Alcohol) Topical Sponge	Look alike	0.7%/74%	One application as needed	<p>Orthographic differences in the names, in conjunction with differences in product characteristics, minimize the likelihood of medication error in the usual practice setting.</p> <p><u>Orthographic:</u> <i>Daliresp has an additional upstroke in the name which is absent in Duraprep</i> <i>Duraprep has an additional downstroke in the name which is absent in Daliresp</i></p> <p><u>Dose:</u> <i>One tablet or 500 mcg vs. one application</i></p> <p><u>Dosage form:</u> <i>Tablet vs. topical sponge</i></p> <p><u>Route of Administration:</u> <i>Oral vs. topical</i></p> <p><u>Regulatory Status:</u> <i>Prescription vs. over the counter</i></p>
Dallergy (Chlorpheniramin Phenylephrine, and Methscopolamine) Tablets and Oral Syrup	Look alike	Extended release caplets: 12 mg- 20mg- 2.5 mg Tablets: 4 mg- 10 mg- 1.25 mg Syrup: 2 mg/8 mg/0.75 mg per 5 mL	1/2 to 1 tablet every 12 hours or 5-10 mL every 4 to 6 hours	<p>Orthographic differences in the names, in conjunction with differences in product characteristics, minimize the likelihood of medication error in the usual practice setting.</p> <p><u>Orthographic:</u> <i>Dallergy has an additional upstroke 'l' and an additional downstroke 'g' in the name which is absent in Daliresp</i></p> <p><u>Frequency:</u> <i>Once daily vs. every 12 hours or 4 to 6 hours</i></p>

Appendix I: Risk of medication errors due to product confusion minimized by dissimilarity of the names or specified product characteristics

Proposed name: Daliresp (Roflumilast) Tablets	Strength: 500 mcg	Usual Dose: 1 tablet daily
Failure Mode: Name confusion	Causes	Prevention of Failure (name confusion) Leading to a Medication Error
<p>Dalmane (Flurazepam) Capsules</p> <p>Strength: 15 mg 30mg</p> <p>Dose; 15 to 30 mg once daily at bedtime</p>	<p>Orthographic Similarities: Both names start with Identical letters ‘Dal’</p> <p>Overlap in Dose: Both drugs can be ordered as one tablet/capsule</p> <p>Overlap in Route: Both products are taken Orally</p> <p>Overlap in Frequency: Both products can be ordered as once daily</p>	<p>Orthographic differences in the names, in conjunction with differences in product characteristics, minimize the likelihood of medication error in the usual practice setting.</p> <p>Rationale: Daliresp contains a downstroke 'p' in the name which is absent in Dalmane giving the two names different shape.</p> <p>Dalmane is available is two strengths which needs to be specified on an order. None of the available strengths overlaps with Daliresp.</p>
<p>Diabinese (Chlopropamide) Tablets</p> <p><u>Strength:</u> 100 mg 250 mg</p> <p><u>Dose:</u> One tablet once daily</p>	<p>Orthographic Similarities: Both names start with the similar prefixes</p> <p>Overlap in Dose: Both drugs can be ordered as one tablet</p> <p>Overlap in Route: Both products are taken orally</p> <p>Overlap in Frequency: Both products can be dosed as once daily</p>	<p>Orthographic differences in the names, in conjunction with differences in product characteristics, minimize the likelihood of medication error in the usual practice setting.</p> <p>Rationale: Daliresp contains a downstroke ‘p’ at the end of the name which is absent in Diabinese giving the two names different shape.</p> <p>An order for Diabinese will require a strength as it is available in multiple strengths vs. Daliresp which is available in single strength. There is no numerical overlap in strengths between Daliresp and Diabinese</p>

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/s/

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