CENTER FOR DRUG EVALUATION AND RESEARCH

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PROPRIETARY NAME REVIEW(S)

Department of Health and Human Services

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Center for Drug Evaluation and Research

Office of Surveillance and Epidemiology

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Through:	Irene Z. Chan, PharmD, BCPS, Acting Team Leader Carol A. Holquist, RPh, Director Division of Medication Error Prevention and Analysis (DMEPA)
From:	Loretta Holmes, BSN, PharmD, Safety Evaluator Division of Medication Error Prevention and Analysis (DMEPA)
Subject:	Proprietary Name Review
Drug Name(s):	Dificid (Fidaxomicin) Tablets 200 mg
Applicant/sponsor:	Optimer Pharmaceuticals, Inc.
OSE RCM #:	2010-2648

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

CONTENTS

EXECUTIVE SUMMARY

This review summarizes DMEPA's evaluation of Optimer Pharmaceutical Inc.'s proposed proprietary name, Dificid, for Fidaxomicin Tablets, 200 mg.

Our proprietary name risk assessment 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, Dificid, acceptable for this product. The proposed proprietary name must be re-reviewed 90 days before approval of the NDA.

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. The Applicant will be notified of this finding via letter.

1 BACKGROUND

1.1 INTRODUCTION

This review responds to a December 14, 2010 request from Optimer Pharmaceuticals, Inc. for assessment of the proposed proprietary name, Dificid, regarding potential name confusion with other proprietary or established drug names in the usual practice settings and promotional concerns. Additionally, the container labels, carton labeling and insert labeling are being evaluated for their potential contribution to medication errors under separate cover (OSE Review 2010-2650).

1.2 REGULATORY HISTORY

DMEPA previously reviewed the proposed proprietary name, Dificid, under IND 064435 (OSE Review 2008-1615, dated May 6, 2009.

1.3 PRODUCT INFORMATION

Dificid is an antibacterial indicated in adults 18 years of age and older for treatment of *Clostridium Difficile* infection, also known and *Clostridium difficile*-associated diarrhea, and prevention of recurrences. The recommended dosage is 200 mg twice daily for 10 days with or without food.

Dificid will be supplied in 20-count and 60-count bottles as well as cartons containing ten 10-count blisters (100 tablets). The storage recommendation is 20ºC-25ºC (68ºC-77ºC).

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, 2.2 and 2.3 identify specific information associated with the methodology for the proposed proprietary name, Dificid.

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]

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

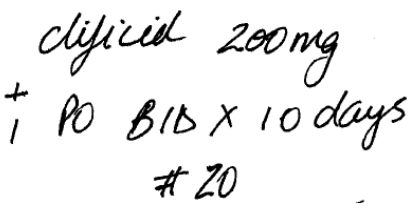
To identify drug names that may look similar to Dificid, the DMEPA Safety Evaluators also consider the orthographic appearance of the name on lined and unlined orders. Specific attributes taken into consideration include the length of the name (seven letters), upstrokes (three, Capital 'D', lower case 'f' and 'd'), downstrokes (one potential, lower case 'f'), cross strokes (one potential, lower case 'f'), and dotted letters (three, lower case 'i'). Additionally, several letters in Dificid may be vulnerable to ambiguity when scripted (see Appendix B). As a result, the DMEPA Safety Evaluators also consider these alternate appearances when identifying drug names that may look similar to Dificid.

When searching to identify potential names that may sound similar to Dificid, the DMEPA Safety Evaluators search for names with similar number of syllables (three), stresses (DI-fi-sid, di-FI-sid, or di-fi-SID), and placement of vowel and consonant sounds. Additionally, the DMEPA Safety Evaluators consider that pronunciation of parts of the name can vary (see Appendix B). The Applicant's intended pronunciation of the name is "'**Di**-fi-sid". However, names are often mispronounced and/or spoken with regional accents and dialects, so other potential pronunciations of the name are considered.

2.2 FDA 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.

Figure 1. Dificid Prescription Studies (conducted on January 5, 2011)

HANDWRITTEN REQUISITION MEDICATION ORDER	VERBAL PRESCRIPTION
Inpatient Medication Order: 	"Dificid 200 mg by mouth twice daily for ten days"
Outpatient Prescription: 	

2.3 NAME SIMILARITY RISK ASSESSMENT POLL

To further assist in determining the overall risk of confusion between Dificid and a specific name, the reviewing Safety Evaluator conducted a poll of the DMEPA staff to determine if they had concerns with the orthographic and/or phonetic similarity of these two names. The poll questions are listed in Appendix D.

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

3 RESULTS

The following sections describe DMEPA's findings from the database searches, CDER Expert Panel Discussion, FDA prescription analysis studies, and risk assessment poll.

3.1 DATABASE AND INFORMATION SOURCES

The DMEPA searches yielded a total of 44 names as having some similarity to the name Dificid,

Nineteen of these names, Diapid, Diflucan, (b) (4) Definity, Diflunisal, Dilaudid, Dilt-CD, Dycill, Difil-G, Defen LA, Dilantin, Rifadin, Claforan, Ticlid, Desitin, Vepesid, Dyphysin, Prevacid, and Differin were identified and evaluated in our previous review and will not be discussed further since the product characteristics of Dificid have not changed since our previous name review.

Of the 25 remaining names, 23 were thought to look like Dificid. These include (b) (4) Decabid, Disipal, Cefobid, Digifab, Debrox, Dolobid, Desferal, Desyrel, Drysol, Clinoril, Clindagel, Darbid, Dendrid, Dibenil, Duoneb, Duvoid, Dyazide, Synercid, Datscan, Detrol, (b) (4) and Butisol. The remaining two names, Divista and Darvocet, were thought to look and sound similar to Dificid.

Additionally, DMEPA Safety Evaluators did not identify any United States Adopted Names (USAN) stems in the proposed proprietary name as of February 10, 2011.

3.2 CDER EXPERT PANEL DISCUSSION

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

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 FDA PRESCRIPTION ANALYSIS STUDIES

A total of 37 practitioners responded. Seven practitioners interpreted the name correctly as "Dificid" (six in the outpatient study and one in the verbal study). Ten practitioners in the outpatient study interpreted the beginning two letters as "Cl". Two practitioners in the outpatient prescription study interpreted the name as "Diflucan" a currently marketed drug product. Diflucan was evaluated in our previous name review of Dificid (OSE Review 2008-1616, dated May 6, 2009) and it was determined the name was not vulnerable to confusion with Dificid; therefore the name will not be discussed further. See Appendix C for the complete listing of interpretations from the verbal and written prescription studies.

3.4 NAME SIMILARITY RISK ASSESSMENT POLL

In response to the reviewing Safety Evaluator's poll which asked, "Is the name **Clinoril** convincingly similar to **Dificid** such that practitioners would become confused at any point in the usual practice setting? Please respond 'yes' or 'no' and state your rationale". Thirteen staff members responded. Nine of the responses were "no" and four responses were "yes". The results of the poll did not render the name unacceptable. The comments provided by the DMEPA staff members are included in Appendix D.

3.5 COMMENTS FROM THE DIVISION OF ANTI-INFECTIVE AND OPHTHALMOLOGY PRODUCTS (DAIOP)

3.5.1 Initial Phase of Review

In response to the email sent to the Division of Anti-infective and Ophthalmology Products (DAIOP) on December 22, 2010, the Division stated "We have no preliminary concerns regarding the proposed proprietary name."

3.5.2 Midpoint of Review

On February 18, 2011, DMEPA notified DAIOP via e-mail that we had no objections to the proposed proprietary name, Dificid. Per e-mail correspondence from DAIOP on March 2, 2011, the Division stated "Everyone seems to be Ok with the name."

3.6 SAFETY EVALUATOR SEARCHES

Independent searches by the primary Safety Evaluator resulted in identification of three additional names, Dilacor XR, (b) (4) and Diflosid which were thought to look similar to Dificid and represent a potential source of drug name confusion.

Thus, we evaluated a total of 28 new names: 25 identified in Database and Information Sources (Section 3.1) and three identified in this section by the primary Safety Evaluator.

4 DISCUSSION

This proposed name, Dificid, was evaluated from a safety and promotional perspective. Furthermore, input from pertinent disciplines involved with the review of this application was considered accordingly.

4.1 PROMOTIONAL ASSESSMENT

DDMAC evaluated the name Dificid from a promotional perspective and determined the name was acceptable. The Division of Anti-infective and Ophthalmology Products and the Division of Medication Error Prevention and Analysis concurred with this assessment.

4.2 SAFETY ASSESSMENT

In total, 28 names were identified as potential sources of name confusion with the proposed proprietary name, Dificid. DMEPA did not identify other aspects of the name that could function as a source of error. Fourteen of the 28 names were eliminated for the following reasons: seven names lack orthographic and/or phonetic similarity, one is a foreign drug product, four are discontinued products with no generic equivalents, one is an orphan drug not approved for marketing in the U.S., and one name has never been marketed in the U.S. (see Appendices E through I).

Failure mode and effects analysis (FMEA) was then applied to determine if the proposed name could potentially be confused with the remaining 14 names and lead to medication errors.

This analysis determined that the name similarity between Dificid and these 14 products is unlikely to result in medication errors for the reasons presented in Appendices J and K.

5 CONCLUSIONS AND RECOMMENDATIONS

The Proprietary Name Risk Assessment findings indicate that the proposed name, Dificid, is not promotional nor is it vulnerable to name confusion that could lead to medication errors. Thus, the Division of Medication Error Prevention and Analysis (DMEPA) has no objection to the proprietary name, Dificid, for this product at this time.

However, if any of the proposed product characteristics as stated in this review are altered prior to approval of this product, DMEPA rescinds this Risk Assessment finding and the name must be resubmitted for review. In the event that our Risk Assessment finding is rescinded, the evaluation of the name on resubmission is independent of the previous Risk Assessment, and as such, the conclusions on re-review of the name are subject to change. If the approval of this application is delayed beyond 90 days from the signature date of this review, the proposed name must be re-evaluated. If you have further questions or need clarifications, please contact Brantley Dorch, OSE Project Manager, at 301-796-0150.

5.1 COMMENTS FOR THE PROPRIETARY NAME LETTER

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

If the approval of this application is delayed for any reason, the name will be re-reviewed 90 days prior to approval of the NDA. If we find the name unacceptable following the re-review, we will notify you.

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.

6 REFERENCES

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

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

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

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

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

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

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

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

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

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

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

   Provides information regarding patent and trademarks.

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

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

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)***

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)***

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

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

List contains all the recognized USAN stems.

14. ***Red Book Pharmacy's Fundamental Reference***

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

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

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

16. ***Medical Abbreviations Book***

Contains commonly used medical abbreviations and their definitions.

APPENDICES

Appendix A:

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 Safety Evaluators 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 Safety Evaluators also conduct internal CDER prescription analysis studies. When provided, DMEPA considers external prescription analysis study results and incorporate into the overall risk assessment.

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

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 Safety Evaluators 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 Safety Evaluators consider 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 Safety Evaluators consider 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 in spelled names may have greater likelihood to sound similar to one another when spoken or look similar to one another when scripted. DMEPA Safety Evaluators also examine the orthographic appearance of the proposed name using a number of different handwriting samples. Handwritten communication of drug names has a long-standing association with drug name confusion. Handwriting can cause similarly and even dissimilarly spelled drug name pairs to appear very similar to one another. The similar appearance of drug names when scripted has led to medication errors. The DMEPA Safety Evaluators apply 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 Safety Evaluators compare 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.

[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.

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

Type of similarity	**Considerations when searching the databases**		
	Potential causes of drug name similarity	*Attributes examined to identify similar drug names*	*Potential Effects*
Look-alike	Similar spelling	Identical prefix Identical infix Identical suffix Length of the name Overlapping product characteristics	• Names may appear similar in print or electronic media and lead to drug name confusion in printed or electronic communication • Names may look similar when scripted and lead to drug name confusion in written communication
	Orthographic similarity	Similar spelling Length of the name Upstrokes Down strokes Cross-stokes Dotted letters Ambiguity introduced by scripting letters Overlapping product characteristics	• Names may look similar when scripted, and lead to drug name confusion in written communication
Sound-alike	Phonetic similarity	Identical prefix Identical infix Identical suffix Number of syllables Stresses Placement of vowel sounds Placement of consonant sounds Overlapping product characteristics	• Names may sound similar when pronounced and lead to drug name confusion in verbal communication

Lastly, the DMEPA Safety Evaluators also consider 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 Safety Evaluators conduct 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 Safety Evaluators 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 Safety Evaluators 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) Safety Evaluators 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 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 posses similarity that would cause confusion at any point in the medication use system, thus the name is eliminated from further review.

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

> ***"Could the confusion of the drug names conceivably result in medication errors in the usual practice setting?"***

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

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)].

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

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), Joint Commission on Accreditation of Hospitals (JCOAH), and the Institute for Safe Medication Practices (ISMP). These organizations have examined medication errors resulting from look- or sound-alike drug names and called for regulatory authorities to address the issue prior to approval. Additionally, DMEPA contends that the threshold set for the Proprietary Name Risk Assessment is reasonable because proprietary drug name confusion is a predictable and a preventable source of medication error that, in many instances, the Agency and/or Applicant can identify and rectify prior to approval to avoid patient harm.

Furthermore, post-marketing experience has demonstrated that medication errors resulting from drug name confusion are notoriously difficult to rectify post-approval. Educational and other post-approval efforts are low-leverage strategies that have had limited effectiveness at alleviating medication errors involving drug name confusion. Applicants have undertaken higher-leverage strategies, such as drug name changes, in the past but at great financial cost to the Applicant and at the expense of the public welfare, not to mention the Agency's credibility as the authority responsible for approving the error-prone proprietary name. Moreover, even after Applicants' have changed a product's proprietary name in the post-approval phase, it is difficult to eradicate the original proprietary name from practitioners' vocabulary, and as a result, the Agency has continued to receive reports of drug name confusion long after a name change in some instances. Therefore, DMEPA believes that post-approval efforts at reducing name confusion errors should be reserved for those cases in which the potential for name confusion could not be predicted prior to approval. (See Section 4 for limitations of the process).

Appendix B: Letters with possible orthographic or phonetic misinterpretation

Letters in proposed name "Dificid"	When scripted may appear as:	When spoken may be interpreted as:
Capital 'D'	O, T, block B	B, T
lower case 'd'	cl	b, t
lower case 'i'	e, l	Any vowel
lower case 'f'	t, p	ph
lower case 'i'	e, l	Any vowel
lower case 'c'	a,e,i, l	z, ki, s if followed by an e or i
lower case 'i'	e, l	Any vowel
lower case 'd'	cl	b, t
'cid'		'sed'

Appendix C: FDA Prescription Study Responses

Inpatient Medication Order	Outpatient Medication Order	Voice Prescription
?	Diflucan	Defacet
??	Diflucan?	Devisid
Omturd	clificial	Difacid
Onturd	Clificid	Difficid
Onturd	Clificid	Dificid
oxyturd	Clificid	Dipisid???She speaks too fast - can't understand what she said
Roturd	Clificid	Dipizid
	Clificid	diviset
	Clificid	Syphvacide
	Clificid	Syvicid
	Clificid	Unable to determine the drug name
	Clificiel	
	Dificid	
	Dificid	
	Dificid	

Inpatient Medication Order	Outpatient Medication Order	Voice Prescription
	Dificid	
	dificid	
	Dificid	
	Dijicid	

Appendix D: Safety Evaluator Poll Responses

Poll Question	"Is the name Clinoril convincingly similar to Dificid such that practitioners would become confused at any point in the usual practice setting?	Why or why not?
Staff Responses	No	I could not make these two names look alike with my handwriting sample (under your door) so I do not think they are convincingly similar. Have you done a drug usage for Clinoril? Do prescribers still use this name? Just wondering about the likelihood of the names being confused.
	No	Although a lower case "D" looks similar to 'cl'. The scripted lower case letter 'f' in Dificid differentiates the two names since it is considered an upstroke and downstroke when scripted. Even when printed, it is considered an upstroke letter, which still differentiates the two names.
	No	Rationale: The 'f' in the middle of 'dificid' prevents orthographic similarity to 'clinoril'. Also, there is no phonetic similarity.
	No	When I script the two words, the letter string "Cli-" lacks orthographic similarity with the letter string "Dif-". Also, the letter string "-ril" does not share orthographic similarity with the letter string "-cid".
	No	Although, if you write the name, Dificid, with a lower case letter 'd', the letter strings 'cli-' and '-ri-' in Clinoril may appear similarly to the letter string 'di-' and '-ci-' in Dificid, the remaining of the letters lack orthographic similarity with each other. Additionally, depending on how the letter string 'f' is scripted, the name, Dificid contains an additional down stroke or an upstroke that Clinoril does not contain.

Poll Question	"Is the name Clinoril convincingly similar to Dificid such that practitioners would become confused at any point in the usual practice setting?	Why or why not?
	No	- 'Cl' and 'D' do not appear similar b/c the curvature of the letters is in a different direction - Dificid has a cross-stroke vs. Clinoril does not have a cross-stroke - Dificid has an upstroke in the middle of the name vs. Clinoril has the upstrokes only on the ends of the name.
	No	Dificid includes the letter 'f' in the middle of the name which provides an upstroke and may provide a down stroke or cross stroke when scripted not seen in Clinoril.
	No	The third letter 'f' can be scripted as an upstroke or an downstroke. In both cases, this letter provides differentiation not presented in Clinoril, which does not contain an upstroke or a downstroke in a similar letter position.
	No	Reasoning- Clin and Dif are very distinct beginning sounds, to me. The endings of the names are also very different (ril vs cid)
	Yes	when Dificid is scripted with an open lower case 'd' it looks like Clinoril
	Yes	Both names start and end with similar looking letters. 'Cli' and 'di' can appear similar when scripted. Additionally 'ril' and 'cid' can appear similar when scripted. The only differentiating letter is n vs. f , although f introduces an upstroke and a downstoke, depending on how is it written may not be sufficient to differentiate the name.
	Yes	Both names are similar in length (7 vs.. 8 letters). When Dificid is written in all lower case, the lower case "d" looks similar to lower case "cl" and the the up strike "d" is similar to the up strike "l" in the end; thus the two names appears to share the same beginning and ending. Although there is one up strike "f" in the middle of the name Dificid, the "f" may not always be written very tall; hence both names may share similar shape. Furthermore, the Cambridge study showed that humans only need the beginning and the end of a word in order to read, thus making the middle letters less of a determining factor.
	Yes	The phonetics are different but both could possibly be scripted to appear similar (this is only if the down stroke of the"f" in Dificid is shorten.)

Appendix E: **Names Lacking Orthographic and/or Phonetic Similarity.**

Name	Similarity to Dificid
Debrox	Look
Clindagel	Look
Duoneb	Look
Duvoid	Look
Dyazide	Look
Synercid	Look
Divista	Sound

Appendix F: **Proprietary or Established Names used only in Foreign Countries**

Proprietary Name	Similarity to Dificid	Country	Description
Diflosid	Look and Sound	Pakistan	Drug Class: Antirheumatic Non-steroidal Plain. Established name not available.

Appendix G: **Drug products that are discontinued and no generic equivalent is available**

Proprietary Name	Similarity to Dificid	Status and Date
(b) (4)		

Appendix H: Orphan Drug not approved for marketing in the U.S.

Name	Similarity to Dificid	Comments
(b) (4)		

Appendix I: Name never marketed in the Us.

Name	Similarity to Dificid	Comments
(b) (4)		

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

Appendix J: Products with multiple differentiating product characteristics and/or orthographic/phonetic differences

Product name with potential for confusion	**Similarity to Dificid**	**Strength**	**Signa**	**Name confusion is prevented by the combination of stated product characteristics, orthographic and/or phonetic differences as described** **(Dificid vs. Product)**
Dificid	**N/A**	**200 mg**	**200 mg (1 tablet) orally twice daily for 10 days**	**N/A**
[redacted]				(b) (4)
Digifab (Digoxin Immune Fab, ovine) for Injection	Look	40 mg	Acute ingestion of unknown amount of digoxin: 800 mg intravenously once Acute ingestion of known amount of digoxin: Dose based on number of tablets ingested, e.g., 25 tablets ingested requires 10 vials (400 mg) intravenously	The three ending letters look different ("cid" vs. "fab"). Route of administration: Oral vs. intravenous infusion Frequency of administration: twice daily vs. once or once and repeat if needed Strength: 200 mg vs. 40 mg Dosage form: Tablets vs. for injection

Product name with potential for confusion	**Similarity to Dificid**	**Strength**	**Signa**	**Name confusion is prevented by the combination of stated product characteristics, orthographic and/or phonetic differences as described** **(Dificid vs. Product)**
Dificid	**N/A**	**200 mg**	**200 mg (1 tablet) orally twice daily for 10 days**	**N/A**
Desferal (Desferoxime Mesylate) for Injection	Look	500 mg and 2 g	Acute iron intoxication: 1 g intramuscularly, then 500 mg every 4 to 12 hours based on clinical response or 1 g intravenously, once, followed by 500 mg ever 4 hours for 2 doses Chronic iron overload: Intramuscular: 500 mg to 1 g/day. Give an additional 2 g intravenously with, but separate from, each unit of blood. Subcutaneous: 1 to 2 g/day (20 to 40 mg/kg/day) over 8 to 24 hours with continuous mini-infusion pump	Two letters precede the letter "f" in Dificid as compared to three in Desferal. Route of administration: Oral vs. intravenous, intramuscular, or subcutaneous Strength: 200 mg vs. 500 mg and 2 g Dosage form: Tablets vs. for injection
Desyrel (Trazodone) Tablets *Desyrel has been discontinued. Generics are available.*	Look	50 mg, 100 mg, 150 mg, and 300 mg	Initially, 150 mg per day in divided doses. Increase by 50 mg per day every 3 to 4 days to a dose of 400 mg to 600 mg per day given in divided doses	Dificid contains two upstroke letters whereas Desyrel has one. Dificid contains three dotted letters whereas Desyrel has none. Additionally, the inflix "-fic-" does not look like "-syr-". Strength: 200 mg vs. 50 mg, 100 mg, 150 mg, and 300 mg Desyrel is available in multiple strengths so the strength would have to be specified on a prescription whereas Dificid is available in a single strength and thus the strength would not have to be specified on a prescription.

Product name with potential for confusion	**Similarity to Dificid**	**Strength**	**Signa**	**Name confusion is prevented by the combination of stated product characteristics, orthographic and/or phonetic differences as described** **(Dificid vs. Product)**
Dificid	**N/A**	**200 mg**	**200 mg (1 tablet) orally twice daily for 10 days**	**N/A**
Drysol (Aluminum Chloride, hexahydrate) Solution	Look	20%	1 application every night at bedtime	Dificid contains two upstroke letters whereas Drysol has one. Dificid contains three dotted letters whereas Drysol has none. Route of administration: Oral vs. topical Frequency of administration: Twice daily vs. once daily at bedtime Dosage form: Tablets vs. topical solution
Dendrid (Idoxuridine) Ophthalmic solution	Look	0.1%	One drop into the affected eye(s) every hour; every 2 hours; or four times per day	The first upstroke letter "f" in Dificid does not look similar to the first upstroke letter "d" in Dendrid. Route of administration: Oral vs. ocular Frequency of administration: Twice daily vs. every hour; every 2 hours; or four times per day Dosage form: Tablets vs. ophthalmic solution
Dibenil (Diphenhydramine HCl) Elixir *Dibenil was a branded generic product. Application status 1996: application withdrawn FR effective.*	Look	12.5 mg/5 mL	25 mg (10 mL or 2 teaspoonsful) to 50 mg (20 mL or 4 teaspoonsful) orally every 4 to 6 hours as needed; 50 mg orally at bedtime as needed	Frequency of administration: Twice daily vs. every 4 to 6 hours as needed or at bedtime as needed Prescriptions for Dibenil would have to state the dose in terms of teaspoonsful, milliliters, or milligrams which would help to differentiate it from Dificid because the doses do not overlap. The name Dibenil could not be found in our drug usage databases, so it is unlikely prescriptions are being written using this name.

Product name with potential for confusion	**Similarity to Dificid**	**Strength**	**Signa**	**Name confusion is prevented by the combination of stated product characteristics, orthographic and/or phonetic differences as described** **(Dificid vs. Product)**
Dificid	**N/A**	**200 mg**	**200 mg (1 tablet) orally twice daily for 10 days**	**N/A**
Dilacor XR (Diltiazem HCl) Extended-release Capsules	Look	120 mg, 180 mg, and 240 mg	180 mg to 480 mg orally once daily	Dificid contains two upstroke letters whereas Dilacor has one. The modifier "XR" will help to differentiate the name when it is written. Strength: 200 mg vs. 120 mg, 180 mg, and 240 mg Frequency of administration: Twice daily vs. once daily
Datscan (Ioflupane I 123) Injection	Look	74 MBq (2 mCi) per mL at calibration	111 to 185 MBq (3 mCi to 5 mCi) intravenously once	Dificid contains two upstroke letters whereas Datscan has one. Dificid contains three dotted letters whereas Datscan has none. Route of administration: Oral vs. intravenous Frequency of administration: Twice daily vs. once Dosage form: Tablets vs. injection Context of use: Datscan is an imaging agent used in a radiology setting whereas Dilacor would not be used in that context.
Detrol (Tolterodine Tartrate) Tablets	Look	1 mg and 2 mg	1 mg or 2 mg orally twice daily	The ending letters ("icid" vs. "rol") look different. Dificid contains three dotted letters whereas Detrol has none. Strength: 200 mg vs. 1 mg and 2 mg
Butisol Sodium (Butabarbital Sodium) Tablets Elixir	Look	Tablets: 30 mg and 40 mg Elixir: 30 mg/5 mL	50 mg to 100 mg at bedtime as needed; 15 mg to 30 mg three to four times per day Pre-operative: 50 mg to 100 mg 60 to 90 minutes before surgery. Children: 2 mg to 6 mg per kg, maximum of 100 mg	Dificid contains three dotted letters whereas Butisol has one. Frequency of administration: Twice daily vs. once, once daily, three times per day, or four times per day Strength: 200 mg vs. 30 mg, 40 mg, or 30 mg/5 mL

Product name with potential for confusion	**Similarity to Dificid**	**Strength**	**Signa**	**Name confusion is prevented by the combination of stated product characteristics, orthographic and/or phonetic differences as described** **(Dificid vs. Product)**
Dificid	**N/A**	**200 mg**	**200 mg (1 tablet) orally twice daily for 10 days**	**N/A**
Darvocet A-500 Darvocet N-50 Darvocet N-100 (Propoxyphene and Acetaminophen) Tablets *In November 2010, the FDA requested a voluntary withdrawal of all products containing Propoxyphene due to safety concerns.*	Look	Darvocet A-500 (100 mg/500 mg) Darvocet N-50 (50 mg/325 mg) Darvocet N-100 (100 mg/650 mg)	Darvocet A-500 and Darvocet N-100: One tablet orally every 4 to 6 hours as needed Darvocet N-100: 2 tablets orally every 4 to 6 hours	Dificid contains three dotted letters whereas Darvocet has none. Dificid has two upstroke letters whereas Darvocet has one. All of the Darvocet names have a modifier which would have to be specified on a prescription. Frequency of administration: Twice daily vs. every 4 to 6 hours as needed

Appendix K: Risk of medication errors due to product confusion minimized by the reasons described

Proprietary Name: **Dificid**	**Strength: 200 mg**	**Signa: 200 mg (1 tablet) orally twice daily for 10 days**
Failure Mode: Name confusion	**Causes (could be multiple)**	**Rationale**
Dolobid (Diflunisal) Tablets *Strength:* 500 mg *Dosage:* 1,000 mg orally initially, followed by 500 mg orally every 8 to 12 hours; 250 mg to 1500 mg orally in divided doses	Orthographic similarity: Both names contain seven letters, begin with the letter "D" and end with the letters "id". Both products are available in a single strength so the strength is not required on a prescription. Both products can be administered orally twice daily.	Medication errors unlikely to occur due to orthographic differences between the names. *Rationale:* Dificid contains two upstroke letters whereas Dolobid contains three. Dificid contains three dotted letters whereas Dolobid has one.
Clinoril (Sulindac) Tablets *Strength:* 200 mg *Dosage:* 200 mg (1 tablet) orally twice daily	Orthographic similarity: The beginning letter "D" in Dificid may look similar to the beginning letters "cl" in Clinoril. Both names end with an upstroke letter. Both products have an overlapping strength, dose, and frequency of administration.	Medication errors unlikely to occur due to orthographic differences between the names. *Rationale:* When printed, the letter "f" has an upstroke and cross-stroke presentation which is not present in the upstroke letter "l" in Clinoril. Dificid has three dotted letters whereas Clinoril has two. When written in script, the letter "f" has an upstroke and downstroke presentation which is not characteristic of any of the letters in Clinoril. This may help to differentiate the names orthographically.

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