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

Date:	August 4, 2009
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From:	Zachary Oleszczuk, PharmD, Safety Evaluator Division of Medication Error Prevention and Analysis (DMEPA)
Subject:	Proprietary Name Review
Drug Name(s):	Folotyn (Pralatrexate Injection) 20 mg/mL
Application Type/Number:	NDA # 22-468
Sponsor:	Allos Therapeutics, INC.
OSE RCM #:	2009-1048

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

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EXECUTIVE SUMMARY

Folotyn is the proposed proprietary name for pralatrexate injection. 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 it accordingly. 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 Folotyn conditionally acceptable for this product. DMEPA considers this a final review; however, if approval of the NDA is delayed beyond 90 days from the date of this review, the proposed proprietary name, Folotyn, must be re-evaluated.

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 is in response to a request from Allos Therapeutics, INC to evaluate the proposed proprietary name for its promotional nature and the potential to contribute to medication errors. The proprietary name, Folotyn, is evaluated to determine if the name could be potentially confused with other proprietary or established drug names and whether or not it is promotional.

1.2 PRODUCT INFORMATION

Folotyn (pralatrexate injection) is an antineoplastic agent indicated for relapsed or refractory peripheral T-cell lymphoma (PTCL). The recommended dose of Folotyn is 30 mg/m^2 by intravenous bolus once weekly. Folotyn is given in 7 weeks cycles consisting of six consecutive weeks of therapy followed by one week of rest. Folotyn will be supplied in individual vials of a concentration of 20 mg/mL in 1 mL and 2 mL vials. Folotyn is stored at 2°- 8°C (36 °- 46 °F).

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, Folotyn.

2.1 SEARCH CRITERIA

For this review, particular consideration was given to drug names beginning with the letter 'F' 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

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

To identify drug names that may look similar to 'Folotyn', the DMEPA staff also considers the orthographic appearance of the name on lined and unlined orders. Specific attributes taken into consideration include the length of the name (seven letters), upstrokes (3, capital letter 'F' and lower case letters 'l' and 't'), downstrokes (1, lower case 'y'), and crosstrokes (2, capital 'F' and lower case letter 't') . Additionally, several letters in Folotyn 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 Folotyn.

When searching to identify potential names that may sound similar to Folotyn, the DMEPA staff searches for names with similar number of syllables (Three), stresses (Fol-o-tin, fol-O-tin, or fol-o-TIN), and placement of vowel and consonant sounds. Additionally, the DMEPA staff considers that pronunciation of parts of the name can vary (See Appendix B). Furthermore, 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. Folotyn Study (conducted on June 12, 2009)

HANDWRITTEN REQUISITION MEDICATION ORDER	VERBAL PRESCRIPTION
Inpatient Medication Order: Folotyn 75mg IV q week	Folotyn 57 mg dispene #6. give iv push q week
Outpatient Prescription: Folotyn 57mg (30mg/m²) IV q week	

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

3.1 DATABASE AND INFORMATION SOURCES

The searches yielded a total of 22 names as having some similarity to the name Folotyn.

Ten of the 22 names (Folnate, Tolectin, (b) (4) Follistim, Tikosyn, (b) (4), Fototar, Zoloft, Folasic, and Tolargin) were thought to look like Folotyn. Seven names (Follutien, Folamin, Folatine, Folacin-800, Folerin, Folifem, and Foligan) were thought sound similar to Folotyn. The remaining five names (Foltrin, Solodyn, Folacin, Toliken, and (b) (4) were thought to look and sound similar to Folotyn.

A search of the United States Adopted Name stem list on June 6, 2009 did not identify any United States Adopted Names (USAN) stem within the proposed name, Folotyn.

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 Folotyn.

DDMAC had no concerns regarding the proposed name from a promotional perspective, however DDMAC noted that the name Focalin sounded similar to the proposed name Folotyn. DMEPA did not identify this name during our database search and thus, will included the name Focalin in the analysis of Folotyn.

3.3 FDA PRESCRIPTION ANALYSIS STUDIES

A total of 18 practitioners responded. Nine (n=9) respondents interpreted the name correctly as 'Folotyn', with correct interpretation occurring in the written outpatient studies. The remainder of the responses misinterpreted the drug name. The majority of misinterpretations occurred in the inpatient study, with the first syllable 'Fol-' being misinterpreted as 'Fal-', 'Full-', or 'Fel' and the last syllable '-tyn' being misinterpreted as '-tya' and '-tin'. See Appendix C for the complete listing of interpretations from the verbal and written prescription studies.

Additionally, one respondent in the prescriptions study noted that the proposed name 'Folotyn is too close Solodyn". DMEPA also identified this name during our database search and will included the name Solodyn in the analysis of Folotyn.

3.4 EXTERNAL STUDY

In the proposed name risk assessment submitted by the Sponsor, the Drug Safety Institute (DSI) identified and evaluated a total of 77 drug names (Albutein, Ambien, Bentyl, Celontin, Coloctyl, Copaxone, Dolotic, Enbrel, Feldene, Femhrt, Fentanyl, (b) (4), Fetrin, Flagyl, Flolan, Flomax, Flovent, Floxin, Flucaine, Fluocin, Fluothane, Flurosyn, Flutex, (b) (4) Focalin, (b) (4) Folbalin, Folbic, Folgard, Folic Acid, Folicet, Folinic Acid, Folitab 500, Follistim, Follutein, Foltabs800, Foltrate, Foltrin, Foltx, Folvite, Fortaz, Fosamax, Fototar, Fulvicin, Ilotycin, Isoleucine, Levulan, Lodosyn, Lurotin, Lutein, Magnacet, Mirapex, Motofen, Napholine, Norlutin, Oxybutynin, Phoslo, Polocaine, Poly Otic, Saletin, (b) (4), SFC Lotion, Sloprin, Solatene, Solfoton, Solodyn, Solotuss, (b) (4) Sultrin, Terazol, Triazolam, U-lactin, Ultane, Volitane, Voltaren, Xigris, and Zenapax) that were thought to have some look-alike and/or sound-alike qualities and potential for confusion with Folotyn.

Six of the 77 names (Follistim, Fototar, Follutien, Foltrin, Focalin, and Solodyn) were previously identified in DMEPA Staff searches and the Expert Panel Discussion.

3.5 COMMENTS FROM THE DIVISION OF DRUG ONCOLOGY PRODUCTS (DDOP)

In response to the OSE e-mail on June 10, 2009, DDOP did note that the proposed name Folotyn is phonetically similar to the name Photofrin. Since Photofrin was not identified by any of the DMEPA searches or the external study submitted by the Applicant, the name Photofrin was added to the assessment of the proposed name Folotyn.

DMEPA notified DDOP via e-mail on July 7, 2009, that we had no objections to the proposed proprietary name Folotyn. Per e-mail correspondence from the DDOP on July 14, 2009, they indicated they concur with our assessment of the proposed proprietary name, insert Folotyn.

3.6 SAFETY EVALUATOR RISK ASSESSMENT

Independent searches by the primary Safety Evaluator identified three additional names (Foltabs 90 Plus DHA Foltabs Prenatal, and Folamin) thought to look and/or sound similar and represent a potential source of confusion to Folotyn.

Although Folamin was identified in DMEPA's database search, Folamin, was noted to be a proprietary name for two different products. As such, a total of 98 names were analyzed to determine if the drug names could be confused with Folotyn and if the drug name confusion would likely result in a medication error in the usual practice setting.

4 DISCUSSION

4.1 PROPRIETARY NAME RISK ASSESSMENT

DDMAC did not have any concerns with the proposed name from a promotional perspective, but noted that the same Focalin sounded similar to the proposed name Folotyn. We agree that Focalin sounds similar to Folotyn, and also note that the name Focalin has some orthographic similarity to Folotyn. Thus, we included the name Focalin in our assessment. Additionally, the Division of Drug Oncology Products noted that the name Photofrin sounded similar to Folotyn. We agree with this concern, and included the name Photofrin in our assessment. Thus, DMEPA evaluated a total of 98 names for their potential similarity to the proposed name, Folotyn.

Since Folamin was identified as two separate products with different active ingredient, we evaluated the name Folamin twice using the different active ingredients and different product characteristics for each product. Folamin [1] is used to designate folic acid in Australia, which is no longer actively marketed and Folamin [2] is used to designate the US combination product of cyanocobalamin, folic acid, and pyridoxine.

Seventy (n=70) names were not analyzed further as the names do not have convincing orthographic and/or phonetic similarity and should not result in medication errors with Folotyn (see Appendix D).

The remaining 28 names were determined to have some orthographic and/or phonetic similarity to Folotyn, and thus determined to present some risk for confusion. Failure mode and effects analysis (FMEA) was then applied to determine if the proposed name, Folotyn, could potentially be confused with any of the 28 names and lead to medication errors. This analysis determined that the name similarity between Folotyn was unlikely to result in medication errors with any of the 28 products for the reasons presented in Appendices E through I. This finding was consistent with and supported by an independent risk assessment of the proprietary name submitted by the Applicant. Our findings were shared with DDOP, and the division concurred with our overall assessment of the proposed proprietary name Folotyn.

5 CONCLUSIONS AND RECOMMENDATIONS

The Proprietary Name Risk Assessment findings indicate that the proposed name, Folotyn, is not promotional or 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, Folotyn, 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 the 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 resubmitted for evaluation.

We are willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Sandra Griffith, project manager, at 301-796-2445.

5.1 COMMENTS TO THE APPLICANT

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

If approval is delayed beyond 90 days from the date of this review, the proposed proprietary name must be re-evaluated. If we find the name unacceptable following the re-review, we will notify you..

6 REFERENCES

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

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

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

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

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

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

4. ***AMF Decision Support System [DSS]***

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

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

   This is a list of proposed and pending names that is generated by the Division of Medication Error Prevention and Analysis from the Access database/tracking system.

6. ***Drugs@FDA*** *(http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm)*

   Drugs@FDA contains most of the drug products approved since 1939. The majority of labels, approval letters, reviews, and other information are available for drug products approved from 1998 to the present. Drugs@FDA contains official information about FDA approved brand name, generic drugs, therapeutic biological products, prescription and over-the-counter human drugs and discontinued drugs and "Chemical Type 6" approvals.

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

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

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

   USPTO provides information regarding patent and trademarks.

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

   Clinical Pharmacology contains full monographs for the most common drugs in clinical use, plus mini monographs covering investigational, less common, combination, nutraceutical and nutritional products. It also provides a keyword search engine.

10. ***Data provided by Thomson & Thomson's SAEGIS ™ Online Service, available at*** *(www.thomson-thomson.com)*

The Pharma In-Use Search database contains over 400,000 unique pharmaceutical trademarks and trade names that are used in about 50 countries worldwide. The data is provided under license by IMS HEALTH.

11. ***Natural Medicines Comprehensive Databases*** *(www.naturaldatabase.com)*

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

12. ***Stat!Ref*** *(www.statref.com)*

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

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

USAN Stems List contains all the recognized USAN stems.

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

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

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

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

16. ***Medical Abbreviations Book***

Medical Abbreviations Book contains commonly used medical abbreviations and their definitions

APPENDICES

Appendix A:

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.

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

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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 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. 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.

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

DMEPA will object to the use of proposed proprietary name when the primary Safety Evaluator identifies one or more of the following conditions in the Risk Assessment:

a. DDMAC finds the proposed proprietary name misleading from a promotional perspective, and the Review Division concurs with DDMAC's findings. The Federal Food, Drug, and Cosmetic Act provides that labeling or advertising can misbrand a product if misleading representations are made or suggested by statement, word, design, device, or any combination thereof, whether through a PROPRIETARY name or otherwise [21 U.S.C 321(n); See also 21 U.S.C. 352(a) & (n)].
b. DMEPA identifies that the proposed proprietary name is misleading because of similarity in spelling or pronunciation to another proprietary or established name of a different drug or ingredient [CFR 201.10.(C)(5)].
c. FMEA identifies the potential for confusion between the proposed proprietary name and other proprietary or established drug name(s), <u>and</u> demonstrates that medication errors are likely to result from the drug name confusion under the conditions of usual clinical practice.
d. The proposed proprietary name contains an USAN (United States Adopted Names) stem.
e. DMEPA identifies a potential source of medication error within the proposed proprietary name. For example, the proprietary name may be misleading or, inadvertently, introduce ambiguity and confusion that leads to errors. Such errors may not necessarily involve confusion between the proposed drug and another drug product.

If DMEPA objects to a proposed proprietary name on the basis that drug name confusion could lead to medication errors, the primary Safety Evaluator uses the FMEA process to identify strategies to reduce the risk of medication errors. DMEPA is likely to recommend that the Applicant select an alternative proprietary name and submit the alternate name to the Agency for DMEPA to review. However, in rare instances FMEA may identify plausible strategies that could reduce the risk of medication error of the currently proposed name. In that instance, DMEPA may be able to provide the Applicant with recommendations that reduce or eliminate the potential for error and, thereby, would render the proposed name acceptable.

In the event that DMEPA objects to the use of the proposed proprietary name, based upon the potential for confusion with another proposed (but not yet approved) proprietary name, DMEPA will provide a contingency objection based on the date of approval. Whichever product, the Agency approves first has the right to use the proprietary name, while DMEPA will recommend that the second product to reach approval seek an alternative name.

The threshold set for objection to the proposed proprietary name may seem low to the Applicant. However, the safety concerns set forth in criteria a through e are supported either by FDA regulation or by external healthcare authorities, including the Institute of Medicine (IOM), World Health Organization (WHO), Joint Commission on Accreditation of Hospitals (JCOAH), and the Institute for Safe Medication Practices (ISMP). These organizations have examined medication errors resulting from look- or sound-alike drug names and called for regulatory authorities to address the issue prior to approval. Additionally, DMEPA contends that the threshold set for the Proprietary Name Risk Assessment is reasonable because proprietary drug name confusion is a predictable and a preventable source of medication error that, in many instances, the Agency and/or Applicant can identify and rectify prior to approval to avoid patient harm.

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

Appendix B: Letters with possible orthographic or phonetic misinterpretation

Letters in Name, Folotyn	**Scripted may appear as**	**Spoken may be interpreted as**
Capital 'F'	'J' (Block), 'T', or 'Z'	'V', 'PH', or 'PF'
Lower case 'f'	't' or 'x'	
Lower case 'o'	'a', 'e' or 'u'	'A', 'E', 'I', 'ALL', 'U', or 'Y'
Lower case 'l'	'A', 'b', 'e', 'p' or 's'	
Lower case 't'	'b', 'f', 'r', or 'x'	'D' or 'PT'
Lower case 'y'	'g', 'j', or 'u'	'A', 'E', 'I', 'O', or 'U'
Lower case 'n'	'a', 'h', 'm', 'r', 's', or 'x'	'DN', 'GN', 'KN', 'MN', or 'PN'
Combination of lower case 'yn'	'p'	'IN'

Appendix C: FDA Prescription Study Responses

Inpatient Medication Order	Outpatient Prescription	Voice Prescription
Falotya	Felotyn	Foletin
Falotyn	Folotyn	Foletin
Falotyn	Folotyn	Fullatin
Falotyn	Folotyn	
Folotya	Folotyn	
Folotyn		
Folotyn		
Folotyn		
Folotyn		
Folotyn		

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

Proprietary Name
Folnate
(b) (4)
Follistim
Tikosyn
(b) (4)
Albutein
Ambien
Bentyl
Celontin
Coloctyl
Copaxone
Dolotic
Enbrel
Femhrt
Feldene
Fentanyl
(b) (4)
Fetrin
Flagyl
Flolan

Proprietary Name
Flomax
Flovent
Floxin
Flucaine
Fluocin
Fluothane
Flurosyn
Flutex
(b)
(b) (4)
Folbalin
Folbic
Folgard
Folic acid
Folicet
Folinic acid
Foltrate
Foltx
Folvite
Fortaz
Fosamax
Fulvicin

Proprietary Name
Isoleucine
Levulan
Lurotin
Lutein
Magnacet
Mirapex
Motofen
Napholine
Norlutin
Oxybutynin
Phoslo
Polocaine
Poly Otic
Saletin
(b)
SFC Lotion
Sloprin
Solfoton
Solotuss
(b) (4)
Sultrin

Proprietary Name
Terazol
Triazolam
U-Lactin
Ultane
Voltaren
Xigris
Zenapax

Appendix E: Proprietary names for discontinued products with no generic equivalent or discontinued over-the-counter products.

Proprietary Name	Similarity to Folotyn	Active Ingredients
(b) (4)	Look	(b) (4)

Appendix F: Drug marketed only in foreign countries

Proprietary Name	Active Ingredient	Country
Folasic	Folic Acid	Australia
Tolargin	Atropine methonitrate dipyrone papaverine hydrochloride	Poland
Folamin [1] (in Australia)	Folic Acid	Australia (this product is no longer marketed)
Folatine	Folic Acid	United Kingdom
Folerin	Loratadine	Indonesia
Folifem	Folic Acid	Poland
Foligan	Allopurinol	Germany
Toliken	Clindamycin	Germany

Appendix G: Products with no numeric overlap in dose or strength

Product name with potential for confusion	Similarity to Folotyn	Strength	Effects
Folotyn **(Pralatrexate Injection)**		**20 mg/mL and 40 mg/2 mL**	**Usual Dose:** **30 mg/m^2 intravenous bolus injection given once weekly**
Follutein (chorionic gonadotropin)	Sound	Powder for Injection: 5,000 units/mL, 2,000 units/mL and 1,000 units/mL	IM use only: **Prepubertal cryptorchidism not caused by anatomical obstruction:** 1. 4,000 units 3 times weekly for 3 weeks. Then 2. 5,000 units every second day for 4 injections. Then 3. 15 injections of 500 to 1,000 units over a period of 6 weeks. Then 4. 500 units 3 times weekly for 4 to 6 weeks. If this course of treatment is not successful, another is begun 1 month later, giving 1,000 units/injection. **Selected cases of male hypogonadism secondary to pituitary failure:** 1. 500 to 1,000 units 3 times a week for 3 weeks, followed by the same dose twice a week for 3 weeks. Then 2. 4,000 units 3 times weekly for 6 to 9 months, following which the dosage may be reduced to 2,000 units 3 times weekly for an additional 3 months. **Induction of ovulation and pregnancy:** 5,000 to 10,000 units 1 day following the last dose of menotropins. A dosage of 10,000 units is recommended in the labeling for menotropins.

Appendix H: Products with single strength, overlapping strength or numeric similarity in dose or strength but multiple differentiating product characteristics

Product name with potential for confusion	**Similarity to Proposed Proprietary Name**	**Strength**	**Usual Dose (if applicable)**	**Other differentiating product characteristics**
Folotyn (Pralatrexate Injection)		**20 mg/mL and 40 mg/2 mL**	**Usual Dose: 30 mg/m^2 intravenous bolus injection given once weekly**	
Tolectin (Tolmetin Sodium)	Look	Tablets: 200 mg, 400 mg, and 600 mg	1,200 mg to 1,800 mg orally in three divided doses	Dosage Form (injection vs. tablet) Dose (30 mg/m^2 vs. 400 mg to 600 mg) Frequency of Administration (once weekly vs. three times daily) Route of Administration (intravenous vs. oral)
Zoloft (Sertraline)	Look	Tablets: 25 mg, 50 mg, and 100 mg Oral Solution: 20 mg/mL	50 mg to 200 mg per day once orally	Dosage Form (injection vs. tablet) Dose (30 mg/m^2 vs. 400 mg to 600 mg) Frequency of Administration (once weekly vs. three times daily) Route of Administration (intravenous vs. oral)
Foltabs 800 (Cyanocobalamin, Folic Acid, and Pyridoxine)	Look	Tablets Cyanocobalamin 115 mcg, Folic Acid 800 mcg, and Pyridoxine 10mg	1 tablet orally once daily	Dosage Form (injection vs. tablet) Dose (30 mg/m^2 vs. 1 tablet) Frequency of Administration (once weekly vs. once daily) Route of Administration (intravenous vs. oral)

Appendix H: Products with single strength, overlapping strength or numeric similarity in dose or strength but multiple differentiating product characteristics (continued)

Folitab (Ascorbic Acid 500mg, Ferrous Sulfate 525mg, and Folic Acid 0.8mg)	Look	Ascorbic Acid 500mg, Ferrous Sulfate 525mg, and Folic Acid 0.8mg	One tablet orally once daily	Dosage Form (injection vs. tablet) Dose (30 mg/m^2 vs. 1 tablet) Frequency of Administration (once weekly vs. once daily) Route of Administration (intravenous vs. oral)
(b) (4)				
Fototar (coal tar extract)	Look	Equivalent to 2% coal tar	Apply to affected areas one to four times daily or as directed by a physician	Dosage Form (injection vs. cream) Dose (30 mg/m^2 vs. 1 application) Frequency of Administration (once weekly vs. four times daily) Route of Administration (intravenous vs. topical)
Lodosyn (Carbidopa)	Look	Tablets: 25 mg	12.5 mg to 25 mg orally 1 to 4 times a day as need as an addition to carbidopa and levodopa combination. Max total dose of carbidopa should not exceed 200 mg per day.	Dosage Form (injection vs. tablet) Dose (30 mg/m^2 vs. 12.5 mg to 25 mg) Frequency of Administration (once weekly vs. once to four times daily as needed) Route of Administration (intravenous vs. oral)

Appendix H: Products with single strength, overlapping strength or numeric similarity in dose or strength but multiple differentiating product characteristics (continued)

Foltabs 90 Plus DHA	Look	Tablets: Ascorbic Acid 120 mg, Calcium 200 mg, Cholecalciferol 400 IU, Copper 2 mg, Dl-Alpha Tocopheryl Acetate 30 IU, Docusate Sodium 50 mg, Folic Acid 1 mg, Iodine 150 mcg, Iron 90 mg, Niacinamide 20 mg, Pyridoxine 20 mg, Riboflavin 3.4 mg, Thiamine 3 mg, and Zinc 25 mg	One tablet orally once daily	Dosage Form (injection vs. tablet) Dose (30 mg/m^2 vs. 1 tablet) Frequency of Administration (once weekly vs. once daily) Route of Administration (intravenous vs. oral)
Foltabs Prenatal	Look	Tablets: Ascorbic Acid 120 mg, Calcium 125 mg, Cholecalciferol 400 IU, Copper 2 mg, Dl-Alpha Tocopheryl Acetate 30 IU, Docusate Sodium 50 mg, Folic Acid 1 mg, Iodine 150 mcg, Iron 27 mg, Niacinamide 20 mg, Pyridoxine 20 mg, Riboflavin 3.4 mg, Thiamine 3 mg, and Zinc 25 mg	One tablet orally once daily	Dosage Form (injection vs. tablet) Dose (30 mg/m^2 vs. 1 tablet) Frequency of Administration (once weekly vs. once daily) Route of Administration (intravenous vs. oral)

Appendix H: Products with single strength, overlapping strength or numeric similarity in dose or strength but multiple differentiating product characteristics (continued)

Solatene (beta carotene)	Sound	Capsules: 30 mg	30 mg to 300 orally per day in divided doses	Dosage Form (injection vs. capsule) Frequency of Administration (once weekly vs. once or more per day) Route of Administration (intravenous vs. oral)
Folamin [2] as marketed in the United States (Cyanocobalamin, Folic Acid, and Pyridoxine)	Sound	Tablet: Cyanocobalamin 2 mg, Folic Acid 2.5 mg, Pyridoxine 25 mg	One tablet to two tablets orally once daily	Dosage Form (injection vs. tablet) Dose (30 mg/m^2 vs. one tablet to 2 tablets) Frequency of Administration (once weekly vs. once daily) Route of Administration (intravenous vs. oral)
Folacin (Folic Acid)	Look and Sound	Tablet: 800 mcg	0.8 mg orally once daily	Dosage Form (injection vs. tablet) Dose (30 mg/m^2 vs. 0.8 mg) Frequency of Administration (once weekly vs. once daily) Route of Administration (intravenous vs. oral)
Folacin-800 (Folic Acid)	Look and Sound	Tablet: 800 mcg	0.8 mg orally once daily	Dosage Form (injection vs. tablet) Dose (30 mg/m^2 vs. 0.8 mg) Frequency of Administration (once weekly vs. once daily) Route of Administration (intravenous vs. oral)
Foltrin (Ascorbic Acid, Cyanocobalamin, Ferrous Fumarate, Folic Acid, and Liver Stomach Concentrate)	Look and Sound	Capsule: Ascorbic Acid 75 mg, Cyanocobalamin 15 mcg, Ferrous Fumarate 110mg, Folic Acid 0.5 mg, Liver Stomach Concentrate 240mg	1 to 2 capsules orally once daily	Dosage Form (injection vs. capsules) Dose (30 mg/m^2 vs. one to 2 capsules) Frequency of Administration (once weekly vs. once daily) Route of Administration (intravenous vs. oral)

Appendix H: Products with single strength, overlapping strength or numeric similarity in dose or strength but multiple differentiating product characteristics (continued)

Solodyn (Minocycline Hydrochloride)	Look and Sound	Extended Release Tablets: 45 mg, 90 mg, and 135 mg	45 mg to 135 mg orally once daily	Dosage Form (injection vs. extended release tablet) Frequency of Administration (once weekly vs. once daily) Route of Administration (intravenous vs. oral)
Ilotycin (erythromycin)	Look	Ophthalmic Ointment: 3.5 grams	Apply 1 cm topically to eyes once to six times daily	Dosage Form (injection vs. ophthalmic ointment) Frequency of Administration (once weekly vs. once to six times daily) Route of Administration (intravenous vs. ophthalmic topical)
Focalin (Dexmethylphenidate Hydrochloride)	Look and Sound	Tablets: 2.5 mg, 5 mg, and 10 mg Extended-Release Capsules: 5 mg, 10 mg, 15 mg, and 20 mg	Tablets: 2.5 mg to 10 mg orally twice daily. Extended-Release Capsules: 5 mg to 20 mg orally once daily	Dosage Form (injection vs. tablets and extended release capsule) Frequency of Administration (once weekly vs. once or twice daily) Route of Administration (intravenous vs. oral)

Appendix I: Potential confusing names with numerical similarity or numerical overlap in dose or strength

Failure Mode: Name confusion	**Causes (could be multiple)**	**Effects**
Folotyn (Pralatrexate Injection)	**20 mg/mL and 40 mg/2 mL**	**Usual Dose: 30 mg/m^2 intravenous bolus given once weekly**
Photofrin (porfimer sodium) Dosage From: Powder for injection Strength: 75 mg/vial Dose: 2 mg/kg given as a slow intravenous injection (3 minutes to 5 minutes). One course of therapy includes the injection of Photofrin followed by laser light therapy 40 hours to 50 hours after the injection. A second administration of laser light therapy can be give 96 hours to 120 hours after the initial injection. A second course of therapy may be initiated 30 days to 90 days after the second laser light therapy is administered. Up to 3 courses may be given.	Phonetic similarity (both names contain the same number of syllables (3), The beginning ('Fo-' vs. 'Pho-') of each name may sound similar when spoken, and the ending of each name ('-otyn' vs. '-ofrin') may sound similar when spoken. Similar route of administration (intravenous bolus vs. intravenous infusion), similar therapeutic class (chemotherapy), and single concentration products (20 mg/mL vs. 75 mg/vial).	The unlikelihood of the use of verbal orders in the usual practice setting in addition to the difference in frequency and the strength will help to minimize confusion that could lead to medication errors. *Rationale:* Although these names may sound similar when spoken, the use of verbal orders related to chemotherapy agents is not the standard of practice. The Joint Commission has stated that the use of verbal order for antineoplastic agents should be avoided at all times[7]. Since the usual standard of practice would not include the use of verbal orders for either of these two products, it is unlikely that these to products would cause confusion that could lead to medication error. Additionally, the different frequencies (once weekly vs. one dose every 30 days to 90 days for 3 doses) would help to differentiate each product. Similarly the context of use may help to differentiate each product. One instance in which verbal confusion of these two products may occur is doing the procurement process of ordering the medications for stock purposes. If healthcare professionals are placing orders for these medication over the phone there is a possibility these two name could get confusion. However, Folotyn and Photofrin differ in strengths. Folotyn will be supplied in vials containing two different amounts of drug product (20 mg/mL vs. 40 mg/2 mL) and therefore the size of the vials would have to be clarified in the ordering process. Photofrin is only available in one strength (75 mg/vial). The different strengths of the product should help to minimize the risk of confusion between these two products that could lead to medication errors. Although, Photofrin and Folotyn do have phonetic similarities; the usual practice for antineoplastic agents would not included the use of verbal orders. In addition the frequency (once weekly vs. one dose every 30 days to 90 days for 3 doses) and strength (20 mg/mL vs. 75 mg/vial) of each product is different and will help minimize the possibility of error in the usual practice setting.

[7] Joint Commission Guide to Priority Focus Areas. JCR staff, Join Commission. 2004.

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