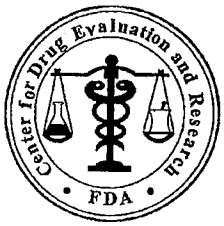
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-387

PROPRIETARY NAME REVIEW(S)



Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	June 29, 2009
To:	Norman Stockbridge, MD Director, Division of Cardiovascular and Renal Products
Through:	Carlos Mena-Grillasca, RPh, Acting Team Leader Denise Toyer, PharmD, Deputy Director Division of Medication Error Prevention and Analysis
From:	Judy Park, PharmD, Safety Evaluator Division of Medication Error Prevention and Analysis
Subject:	Final Proprietary Name Review
Drug Name(s):	Tyvaso (Treprostinil) Inhalation Solution 0.6 mg/mL
Application Type/Number:	NDA 22-387
Applicant:	United Therapeutics Corporation
OSE RCM #:	2009-814

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

CONTENTS

EXECUTIVE SUMMARY

This re-assessment of this proprietary name is written in response to a notification that treprostinil will be approved within 90 days. DMEPA found the proposed proprietary name, Tyvaso, acceptable in OSE Review #2008-1113 on February 19, 2009. Since that review, none of Tyvaso's product characteristics have changed.

During this re-review we identified 9 new names for their similarity to Tyvaso. The results of the Failure Mode Effects Analysis found that the proposed name, Tyvaso, is not vulnerable to name confusion that could lead to medication errors with any of 9 names. Thus, the Division of Medication Error Prevention and Analysis does not object to the use of the proprietary name, Tyvaso, for this product.

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

1 METHODS AND MATERIALS

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

1.1 PROPRIETARY NAME RISK ASSESSMENT

For this review, particular consideration was given to drug names beginning with the letter 'T' 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]

To identify drug names that may look similar to Tyvaso, DMEPA also consider the orthographic appearance of the name on lined and unlined orders. Specific attributes taken into consideration include the length of the name (six letters), upstrokes (one, capital letter 'T'), downstokes (lower case 'y'), cross-strokes (none), and dotted letters (none). Additionally, several letters in Tyvaso may be vulnerable to ambiguity when scripted, including the letter 'T' may appear as 'F,' 'L,' 'S,' 'Z,' or 'A'; lower case 'y' may appear as a lower case 'g' or 'p'; lower case 'v' may appear as 'c,' 'r,' 's,' or 'z'; and 'a' and 'o' may appear as 'a,' 'e,' 'i,' 'o,' or 'u'. As such, the staff also considers these alternate appearances when identifying drug names that may look similar to Tyvaso.

When searching to identify potential names that may sound similar to Tyvaso, the DMEPA staff searches for names with similar number of syllables (three), stresses (ty-VA-so or TY-va-so), and placement of vowel and consonant sounds. Additionally, several letters in Tyvaso may be

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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. Artifical Inteligence in Medicine (2005)

vulnerable to misinterpretation when spoken, including 'Ty' may be interpreted as 'Zy'; 'v' may be interpreted as 'b' and 's' may be interpreted as 'c' or 'z'. As such, the staff also considers these alternate pronunciations when identifying drug names that may sound similar to Tyvaso. The Applicant's intended pronunciation of the proprietary name could not be expressly taken into consideration, as this was not provided with the proposed name submission.

2 RESULTS

2.1 DATABASE AND INFORMATION SOURCES

The searches of the databases listed in Section 6 yielded a total of 19 names as having some similarity to the name Tyvaso.

Seventeen of the 19 names were thought to look like Tyvaso, which include: Lyrica, Lysine, —— Tazorac, Tequin, —— Tyrazol, Tyrex, Tyrex-2, —— Tysabri, Tyverb, Tyzeka, Tyzine, Vyvanse, Zyrona, and Zyvox. One additional name, Tri-Vi-Sol, was thought to sound similar to Tyvaso. One name, Travasol, was thought to look and sound similar to Tyvaso. b(4)

A search of the United States Adopted Names (USAN) stem list on June 22, 2009 identified no USAN stems contained in the proposed name, Tyvaso.

2.2 EXPERT PANEL DISCUSSION

The Expert Panel reviewed the pool of names identified by the DMEPA staff (see section 2.1 above), and noted no additional names thought to have orthographic or phonetic similarity to Tyvaso.

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

2.3 SAFETY EVALUATOR RISK ASSESSMENT

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

Ten of the 19 names were identified in the previous Tyvaso proprietary name review (See Appendix B). None of Tyvaso's product characteristics have changed since the previous review. Therefore, the original assessment is maintained. Please see OSE #2008-1113 for a detailed analysis of these names.

3 DISCUSSION

Nine names were evaluated for their potential similarity to the proposed name, Tyvaso. Four names lacked orthographic and/or phonetic similarity to Tyvaso and were not evaluated further (See Appendix C).

Failure mode and effect analysis (FMEA) was then applied to determine if the proposed name could potentially be confused with the remaining 5 names and lead to medication errors. This analysis determined that the name similarity between Tyvaso was unlikely to result in medication errors with any of the 5 products for the reasons presented in Appendices D and E.

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

4 CONCLUSIONS AND RECOMMENDATIONS

The Proprietary Name Risk Assessment findings indicate that the proposed name, Tyvaso, is not vulnerable to name confusion that could lead to medication errors. As such, we do not object to the use of the proprietary name, Tyvaso, for this product. Additionally, DDMAC does not object to the proposed name, Tyvaso, from a promotional perspective.

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

We are willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Sean Bradley, OSE project manager, at 301-796-1332.

5 REFERENCES

1. Micromedex Integrated Index (http://weblern/)

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 Medication Error Prevention Staff, FDA.

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

Drug Facts and Comparisons is a compendium organized by therapeutic Course; 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 Error Prevention proprietary name consultation requests

This is a list of proposed and pending names that is generated by the Medication Error Prevention Staff 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 and generic drugs and therapeutic biological products; prescription and over-the-counter human drugs and therapeutic biologicals, 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. US Patent and Trademark Office location http://www.uspto.gov.

Provides information regarding patent and trademarks.

9. Clinical Pharmacology Online (http://weblern/)

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 tradenames that are used in about 50 countries worldwide. The data is provided under license by IMS HEALTH.

11. Natural Medicines Comprehensive Databases (http://weblern/)

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

12. Stat!Ref (http://weblern/)

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

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.pharmacist.com)

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

16. Medical Abbreviations Book

Contains commonly used medical abbreviations and their definitions.

17. Prior OSE Review

OSE Review #2008-1113. DMEPA Proprietary Name Review for Tyvaso (Treprostinil) Inhalation Solution, 0.6 mg/mL, Judy Park; February 19, 2009.

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.

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

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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.

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

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.

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

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

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. 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:

1. DDMAC finds the proposed proprietary name misleading from a promotional perspective, and the Review Division concurs with DDMAC's findings. The Federal Food, Drug, and Cosmetic Act provides that labeling or advertising can misbrand a product if misleading representations are made or suggested by statement, word, design, device, or any combination thereof, whether through a PROPRIETARY name or otherwise [21 U.S.C 321(n); See also 21 U.S.C. 352(a) & (n)].

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

2. DMEPA identifies that the proposed proprietary name is misleading because of similarity in spelling or pronunciation to another proprietary or established name of a different drug or ingredient [CFR 201.10.(C)(5)].
3. FMEA identifies 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.
4. The proposed proprietary name contains an USAN (United States Adopted Names) stem.
5. DMEPA identifies a potential source of medication error within the proposed proprietary name. For example, the proprietary name may be misleading or, inadvertently, introduce ambiguity and confusion that leads to errors. Such errors may not necessarily involve confusion between the proposed drug and another drug product.

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

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

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

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

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

Name	Name
Lyrica	Tysabri
Lysine	Tyverb
Travasol	Tyzeka
Tyrex	Tyzine
Tyrex-2	Zyvox

Appendix C: Proprietary names with minimal orthographic and/or phonetic similarity

Proprietary Name	Similarity to Tyvaso
Tazorac	Look
Tequin	Look
[redacted]	Look
Tri-Vi-Sol	Sound

b(4)

Appendix D: Proprietary names used only in foreign countries

Proprietary Name	Similarity to Tyvaso	Country
[redacted]	Look	Philippines
Tyrazol	Look	Finland
Zyrona	Look	Sweden

b(4)

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Appendix E: Products with no overlap in strength or dose

Product name with potential for confusion	Similarity to Proposed Proprietary Name	Strength	Usual Dose (if applicable)
Tyvaso (treprostinil)		**0.6 mg/mL**	**Usual dose: 3 to 9 breaths (18 mcg to 54 mcg) per inhalation session four times daily**
[redacted]		[redacted]	b(4)
Vyvanse (Lisdexamfetamine Dimesylate)	Look	20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg	30 mg (1 tablet) by mouth once in the morning

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

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/s/

Judy Park
6/29/2009 02:34:36 PM
DRUG SAFETY OFFICE REVIEWER

Carlos M Mena-Grillasca
6/29/2009 03:31:11 PM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
7/1/2009 03:57:02 PM
DRUG SAFETY OFFICE REVIEWER

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	February 18, 2009
To:	Norman Stockbridge, MD Director, Division of Cardiovascular and Renal Products
Through:	Kellie Taylor, PharmD, MPH, Team Leader Denise Toyer, PharmD, Deputy Director Carol Holquist, RPh, Director Division of Medication Error Prevention and Analysis
From:	Judy Park, PharmD, Safety Evaluator Division of Medication Error Prevention and Analysis
Subject:	Proprietary Name Review
Drug Name(s):	Tyvaso (Treprostinil Sodium) Inhalation Solution 0.6 mg/mL
Application Type/Number:	NDA 22-387
Applicant:	United Therapeutics
OSE RCM #:	2008-1113

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

CONTENTS

EXECUTIVE SUMMARY

The results of the Proprietary Name Risk Assessment found that the proposed name, Tyvaso, is not vulnerable to name confusion that could lead to medication errors. As such, the Division of Medication Error Prevention and Analysis does not object to the use of the proprietary name Tyvaso, for this product.

However; if any of the proposed product characteristics considered in this evaluation are altered prior to approval of the product, we rescind this Risk Assessment finding, and recommend that the name be resubmitted for review.

1 BACKGROUND

1.1 INTRODUCTION

This review is in response to a request from the Division of Cardiovascular and Renal Products for assessment of the proposed proprietary name, Tyvaso, regarding its potential confusion with other proprietary or established drug names in normal practice settings.

Additionally, the container labels, carton and insert labeling, and device instruction manual were provided and will be evaluated in a separate review.

1.2 REGULATORY HISTORY

The Applicant submitted Viveta*** previously as proposed proprietary name for the proposed product in the IND stage. However, the Division of Medication Error Prevention and Analysis (DMEPA) and the Division of Drug Marketing, Advertising, and Communications (DDMAC) objected to the proposed name, Viveta, in OSE Review #2007-799 dated February 4, 2008.

1.3 PRODUCT INFORMATION

Tyvaso (treprostinil sodium) inhalation solution is a prostacyclin analogue with vasodilatory, antiproliferative, and platelet anti-aggregatory actions, indicated for the treatment of pulmonary arterial hypertension in patients with NYHA Class III — symptoms. Tyvaso is to be administered by inhalation in four separate sessions per day during waking hours, at least 4 hours apart. Treatment starts with 3 breaths (6 mcg/breath) per inhalation session. If 3 breaths are not tolerated, the dose may be reduced to 1 or 2 breaths and subsequently increased to the target dose of 9 breaths per inhalation session, as tolerated. Tyvaso is intended for use with Optineb-ir® nebulizer which is an ultrasonic pulsated inhalation device. Tyvaso is available in 2.9 mL clear low density polyethylene (LDPE) ampules containing 0.6 mg treprostinil/mL. It is packaged as four ampoules in a foil pouch.

b(4)

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

2 METHODS AND MATERIALS

This section describes the methods and materials used by the medication error prevention staff conducting a proprietary name risk assessment (see 2.1 Proprietary Name Risk Assessment). The primary focus is to identify and remedy potential sources of medication error prior to drug approval. The Division of Medication Error Prevention and Analysis (DMEPA) defines a medication error as any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer. [1]

2.1 PROPRIETARY NAME RISK ASSESSMENT

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

For the proprietary name, Tyvaso, the DMEPA staff search a standard set of databases and information sources to identify names with orthographic and phonetic similarity (see Sections 2.1.1 for detail) and held an CDER Expert Panel discussion to gather professional opinions on the safety of the proposed proprietary name (see 2.1.1.2). Our Division also conducts internal CDER prescription analysis studies (see 2.1.2), and, when provided, external prescription analysis studies results are considered and incorporated into the overall risk assessment (see detail 2.1.4).

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

In addition, the product characteristics provide the context for the verbal and written communication of the drug names and can interact with the orthographic and phonetic attributes of the names to increase the risk of confusion when there is overlap, or, in some instances, decrease the risk of confusion by helping to differentiate the products through dissimilarity. As such, the staff consider the product characteristics associated with the proposed drug throughout the risk assessment, since the product characteristics of the proposed drug may provide a context for communication of the drug name and ultimately determine the use of the product in the *usual* clinical practice setting.

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

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

Typical product characteristics considered when identifying drug names that could potentially be confused with the proposed drug name include, but are not limited to established name of the proposed product, the proposed indication, dosage form, route of administration, strength, unit of measure, dosage units, recommended dose, typical quantity or volume, frequency of administration, product packaging, storage conditions, patient population, and prescriber population. Because drug name confusion can occur at any point in the medication use process, the medication error prevention staff considers the potential for confusion throughout the entire U.S. medication use process, including drug procurement, prescribing and ordering, dispensing, administration, and monitoring the impact of the medication.[3]

2.1.1 Search Criteria

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

For this review, particular consideration was given to drug names beginning with the letter '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.[4][5]

To identify drug names that may look similar to Tyvaso, DMEPA also consider the orthographic appearance of the name on lined and unlined orders. Specific attributes taken into consideration include the length of the name (six letters), upstrokes (one, capital letter 'T'), downstokes (lower case 'y'), cross-strokes (none), and dotted letters (none). Additionally, several letters in Tyvaso may be vulnerable to ambiguity when scripted, including the letter 'T' may appear as 'F,' 'Z,' or 'A'; lower case 'y' may appear as a lower case 'g' or 'p'; lower case 'v' may appear as 'c,' 'r,' 's,' or 'z'; and 'a' and 'o' may appear as 'a,' 'e,' 'i,' 'o,' or 'u'. As such, the staff also considers these alternate appearances when identifying drug names that may look similar to Tyvaso.

When searching to identify potential names that may sound similar to Tyvaso, the DMEPA staff searches for names with similar number of syllables (three), stresses (ty-VA-so or TY-va-so), and placement of vowel and consonant sounds. Additionally, several letters in Tyvaso may be vulnerable to misinterpretation when spoken, including 'Ty' may be interpreted as 'Zy'; 'v' may be interpreted as 'b' and 's' may be interpreted as 'c' or 'z' As such, the staff also considers these alternate pronunciations when identifying drug names that may sound similar to Tyvaso. The Applicant's intended pronunciation of the proprietary name could not be expressly taken into consideration, as this was not provided with the proposed name submission.

The staff also consider the product characteristics associated with the proposed drug throughout the identification of similar drug names, since the product characteristics of the proposed drug ultimately determine the use of the product in the clinical practice setting For this review, the medication error prevention staff was provided with the following information about the proposed product: the proposed proprietary name (Tyvaso), the established name (treprostinil

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

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

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

sodium), proposed indication (pulmonary arterial hypertension in patients with NYHA Class III — symptoms), strength (0.6 mg/mL), dose (4 inhalation sessions per day, 9 breaths per session), frequency of administration (four times daily), route (inhalation) and dosage form of the product (inhalation solution). Appendix A provides a more detailed listing of the product characteristics the staff generally takes into consideration. b(4)

Lastly, the DMEPA staff also consider the potential for the proposed name to inadvertently function as a source of error for reasons other than name confusion. Post-marketing experience has demonstrated that proprietary names (or components of the proprietary name) can be a source of error in a variety of ways. As such, these broader safety implications of the name are considered and evaluated throughout this assessment and the medication error prevention staff provide additional comments related to the safety of the proposed name or product based on their professional experience with medication errors.

2.1.1.1 Database and Information Sources

The proposed proprietary name, Tyvaso, was provided to the DMEPA staff to conduct a search of the internet, several standard published drug product reference texts, and FDA databases to identify existing and proposed drug names that may sound-alike or look-alike to Tyvaso using the criteria outlined in 2.1.1. A standard description of the databases used in the searches is provided in Section 7. To complement the process, the medication error 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 findings of the individual Safety Evaluators were then pooled and presented to the Expert Panel.

2.1.1.2 CDER Expert Panel Discussion

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

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

2.1.2 FDA Prescription Analysis Studies

Three separate studies are conducted within the Centers of the FDA for the proposed proprietary name to determine the degree of confusion of Tyvaso with marketed U.S. drug names (proprietary and established) due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. The studies employ a total of 123 healthcare professionals (pharmacists, physicians, and nurses), and attempts to simulate the prescription ordering process. The results are used by the Safety Evaluator to identify any

orthographic or phonetic vulnerability of the proposed name to be misinterepreted by healthcare practitioners.

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

Figure 1. Tyvaso Study (conducted on August 13, 2008)

HANDWRITTEN PRESCRIPITON AND MEDICATION ORDER	VERBAL INPATIENT ORDER
Inpatient Medication Order: Tyvaso Use as directed qid	Tyvaso #1 box Use as directed QID
Outpatient Prescription Order: Tyvaso #1 box Use as directed qid	

2.1.3 Safety Evaluator Risk Assessment of the Proposed Proprietary Name

Based on the criteria set forth in Section 2.1.1, the Safety Evaluator Risk Assessment applies their individual expertise gained from evaluating medication errors reported to FDA to conduct a Failure Mode and Effects Analysis and provide an overall risk of name confusion. Failure Mode and Effects Analysis (FMEA) is a systematic tool for evaluating a process and identifying where and how it might fail.[6] When applying FMEA to assess the risk of a proposed proprietary name, the medication error prevention staff seeks to evaluate the potential for a proposed name to be confused with another drug name as a result of the name confusion and cause errors to occur in the medication use system. FMEA capitalizes on the predictable and preventable nature of medication errors associated with drug name confusion. FMEA allows the Agency to identify the potential for medication errors due to look- or sound-alike drug names prior to approval, where actions to overcome these issues are easier and more effective then remedies available in the post-approval phase.

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

In order to perform an FMEA of the proposed name, the Safety Evaluator must analyze the use of the product at all points in the medication use system. Because the proposed product is not yet marketed, the Safety Evaluator anticipates the use of the product in the usual practice settings by considering the clinical and product characteristics listed in Appendix A. The Safety Evaluator then analyzes the proposed proprietary name in the context of the usual practice setting and works to identify potential failure modes and the effects associated with the failure modes.

In the initial stage of the Risk Assessment, the Safety Evaluator compares the proposed proprietary name to all of the names gathered from the above searches, expert panel evaluation, and studies, and identifies potential failure modes by asking: "Is the name Tyvaso 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 Tyvaso to be confused with another proprietary or established drug name because of look- or sound-alike similarity. If the answer to the question is no, the Safety Evaluator is not convinced that the names posses similarity that would cause confusion at any point in the medication use system and the name is eliminated from further review.

In the second stage of the Risk Assessment, all potential failure modes are evaluated to determine the likely *effect* of the drug name confusion, by asking "Could the confusion of the drug names conceivably result in medication errors in the usual practice setting?" The answer to this question is a central component of the Safety Evaluator's overall risk assessment of the proprietary name. If the Safety Evaluator determines through FMEA that the name similarity would ultimately not be a source of medication errors in the usual practice setting, the name is eliminated from further analysis. However, if the Safety Evaluator determines through FMEA that the name similarity could ultimately cause medication errors in the usual practice setting, the Safety Evaluator will then recommend that an alternate proprietary name be used. In rare instances, the FMEA findings may provide other risk-reduction strategies, such as product reformulation to avoid an overlap in strength or an alternate modifier designation may be recommended as a means of reducing the risk of medication errors resulting from drug name confusion.

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

1. DDMAC finds the proposed proprietary name misleading from a promotional perspective, and the review Division concurs with DDMAC's findings. The Federal Food, Drug, and Cosmetic Act provides that labeling or advertising can misbrand a product if misleading representations are made or suggested by statement, word, design, device, or any combination thereof, whether through a trade name or otherwise. [21 U.S.C 321(n); see also 21 U.S.C. 352(a) & (n)].
2. The DMEPA staff identifies that the proposed proprietary name is misleading because of similarity in spelling or pronunciation to another proprietary or established name of a different drug or ingredient [CFR 201.10.(C)(5)].
3. FMEA identifies potential for confusion between the proposed proprietary name and other proprietary or established drug names, and demonstrates that medication errors are likely to result from the drug name confusion under the conditions of usual clinical practice.

4. The proposed proprietary name contains an USAN stem, particularly in a manner that is contradictory to the USAN Council's definition.
5. The DMEPA staff identifies a potential source of medication error within the proposed proprietary name. The proprietary name may be misleading, or inadvertently introduce ambiguity and confusion that leads to errors. Such errors may not necessarily involve confusion between the proposed drug another drug product.

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

If none of these conditions are met, then the DMEPA staff will not object to the use of the proprietary name. If any of these conditions are met, then our division will object to the use of the proprietary name. The threshold set for objection to the proposed proprietary name may seem low to the Applicant; however, the safety concerns set forth in criteria 1 through 5 are supported either by FDA Regulation or by external healthcare authorities, including the Institute of Medicine, the World Health Organization, the Joint Commission, and the Institute for Safe Medication Practices, that have examined medication errors resulting from look- or sound-alike drug names and called for Regulatory Authorities to address the issue prior to approval.

Furthermore, the medication error prevention staff contends that the threshold set for the Proprietary Name Risk Assessment is reasonable because proprietary drug name confusion is a predictable and preventable source of medication error that, in many instances, can be identified and remedied prior to approval to avoid patient harm.

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

If the DMEPA staff objects to a proposed proprietary name on the basis that drug name confusion could lead to medication errors, the FMEA process is used to identify strategies to reduce the risk of medication errors. Our Division is likely to recommend that the Applicant select an alternative proprietary name and submit the alternate name to the Agency for the medication error prevention staff to review. However, in rare instances FMEA may identify plausible strategies that could reduce the risk of medication error of the currently proposed name,

and so we may be able to provide the Applicant with recommendations that reduce or eliminate the potential for error would render the proposed name acceptable.

3 RESULTS

3.1 PROPRIETARY NAME RISK ASSESSMENT

3.1.1 Database and Information Sources

The searches identified 19 names as having some similarity to the name Tyvaso.

Fifteen of the 19 names were thought to look like Tyvaso, which include: Alvesco, Lyrica, Lysine, Travase, Tyrex-1, Tyrex-2, Tyromex, Tyros 1, Tyrosum, Tysabri, Tyverb, Tyzine, Zavesca, Zycose, and Zyvox. Two additional names (Tao and Triphasil) were thought to sound similar to Tyvaso. Two names (Travasol and Tyzeka) were thought to look and sound similar to Tyvaso.

A search of the United States Adopted Names (USAN) stem list on November 20, 2008 indentified no USAN stems contained in the proposed name, Tyvaso.

3.1.2 Expert Panel Discussion

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

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

3.1.3 CDER Prescription Analysis Studies

A total of 31 practitioners responded, but none of the responses overlapped with any existing or proposed drug names. Thirty-eight percent of the participants (n=12) interpreted the name correctly as "Tyvaso," with correct interpretation occurring more frequently in the written studies. The remainder of the responses misinterpreted the drug name. The majority of misinterpretations occurring in the phonetic prescription study resulted with the consonants reported as 'sil' or 'sa' instead of 'so'; 'i' instead of 'y'; and 'D' and 'L' instead of 'T'. In the written prescription studies, the letter 'o' was misinterpreted as 'e' by six respondents and 'ol' and 'il' by one respondent each, the letter 'T' was misinterpreted as 'L' by two respondents, and 'v' was misinterpreted as 'r' by three respondents. See Appendix B for the complete listing of interpretations from the verbal and written prescription studies.

3.1.4 Safety Evaluator Risk Assessment

Independent searches by the primary Safety Evaluator did not identify any additional names thought to look similar to Tyvaso and represent a potential source of drug name confusion. A total of 19 names were analyzed to determine if the names could be confused with Tyvaso and if the name confusion would likely result in a medication error.

Seven of the 19 identified names were determined to lack sufficient orthographic and/or phonetic similarity to Tyvaso to present a risk of confusion (See Appendix C). The remaining 12 names

were determined to have some orthographic and /or phonetic similarity to Tyvaso, and thus determined to present some risk of confusion.

Failure mode and effect analysis (FMEA) was then applied to determine if the potential name, Tyvaso, could potentially be confused with any of these 19 names and lead to medication errors. This analysis determined that the name similarity between Tyvaso and the identified names was unlikely to result in medication errors for all 19 products for the reasons described in Appendices D through F.

4 DISCUSSION

In total, we evaluated 19 names for their similarities to the proposed name, Tyvaso, but the findings of the FMEA indicate that the proposed name does not appear to be vulnerable to name confusion that could lead to medication errors.

5 CONCLUSIONS AND RECOMMENDATIONS

The Proprietary Name Risk Assessment findings indicate that the proposed name, Tyvaso, is not vulnerable to name confusion that could lead to medication errors. As such, we do not object to the use of the proprietary name, Tyvaso, for this product. Additionally, DDMAC does not object to the proposed name, Tyvaso, from a promotional perspective.

5.1 COMMENTS TO THE DIVISION

We would appreciate feedback of the final outcome of this review. We would be willing to meet with the Division for further discussion, if needed. Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications, please contact Sean Bradley, OSE Project Manager, at 301-796-1332.

5.2 COMMENTS TO THE APPLICANT

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

If **any** of the proposed product characteristics are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

6 REFERENCES

1. Micromedex Integrated Index (http://weblern/)

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 Medication Error Prevention Staff, FDA.

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

Drug Facts and Comparisons is a compendium organized by therapeutic Course; 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 Error Prevention proprietary name consultation requests

This is a list of proposed and pending names that is generated by the Medication Error Prevention Staff 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 and generic drugs and therapeutic biological products; prescription and over-the-counter human drugs and therapeutic biologicals, 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. US Patent and Trademark Office location http://www.uspto.gov.

Provides information regarding patent and trademarks.

9. Clinical Pharmacology Online (http://weblern/)

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 tradenames that are used in about 50 countries worldwide. The data is provided under license by IMS HEALTH.

11. Natural Medicines Comprehensive Databases (http://weblern/)

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

12. Stat!Ref (http://weblern/)

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

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.pharmacist.com)

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

16. Medical Abbreviations Book

Contains commonly used medical abbreviations and their definitions.

APPENDICES

Appendix A:

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

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

Type of similarity	Considerations when searching the databases		
	Potential causes of drug name similarity	Attributes examined to identify similar drug names	Potential Effects
Look-alike	Similar spelling	Identical prefix Identical infix Identical suffix Length of the name Overlapping product characteristics	• Names may appear similar in print or electronic media and lead to drug name confusion in printed or electronic communication • Names may look similar when scripted and lead to drug name confusion in written communication
	Orthographic similarity	Similar spelling Length of the name Upstokes Downstrokes Cross-stokes	• Names may look similar when scripted, and lead to drug name confusion in written communication

		Dotted letters Ambiguity introduced by scripting letters Overlapping product characteristics	
Sound-alike	Phonetic similarity	Identical prefix Identical infix Identical suffix Number of syllables Stresses Placement of vowel sounds Placement of consonant sounds Overlapping product characteristics	• Names may sound similar when pronounced and lead to drug name confusion in verbal communication

Appendix B:

CDER Prescription Study Responses

Inpatient Medication Order	Outpatient Prescription	Verbal Prescription
Tyvase	Tyvaso	Tymassil
Tyvaso	Lyvaso	Tivasa
Tyrasol	Tyvaso	Divasil
Tyvase	Tyvaso	Tyvasil
Tyvase	Tyvaso	Lyraso
Tyrase	Tyvaso	Tyvasil
Tyraso	Tyvase	Tyvasil
Tyvaso	Lyvaso	Tivasil
Tyvaso		
Tyvasil		
Tyvaso		

Tyvaso		
Tyvaso		
Tyvasce		
Tyvaso		

Appendix C: Proprietary names with minimal orthographic and/or phonetic similarity

Proprietary Name	Similarity to Tyvaso
Alvesco	Look
Tyrex-1	Look
Tyrex-2	Look
Tyromex	Look
Tysabri	Look
Zyvox	Look
Tao	Sound

Appendix D: Proprietary names used only in foreign countries

Proprietary Name	Similarity to Tyvaso	Country
Tyverb	Look	International name for Tykerb

Appendix E: Proprietary name of a discontinued product with no generics available

Proprietary Name	Similarity to Tyvaso	Year discontinued
Travase	Look	unable to find date of discontinuation

Appendix F: Products with no overlap in strength or dose

Product name with potential for confusion	Similarity to Proposed Proprietary Name	Strength	Usual Dose (if applicable)
Tyvaso (treprostinil sodium)		**0.6 mg/mL**	**Usual dose: 3 to 9 breaths (18 mcg to 54 mcg) per inhalation session four times daily**
Lyrica	Look	25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 200 mg, 225 mg, 300 mg	150 mg to 600 mg per day in 2-3 divided doses
Lysine	Look	Not available (amino acid)	1.5 g to 3 g by mouth daily as supplement
Travasol	Look/Sound	Injectable: 10%	Depends on the patient's metabolic requirement and clinical response
Triphasil	Sound	0.05 mg/30 mcg, 0.075 mg/40 mcg, 0.125 mg/30 mcg	1 tablet by mouth daily
Tyros I	Look	Formula for infants and toddlers with tyrosinemia	Varies by child
Tyrosum (Facial cleanser)	Look	Liquid: 120 mL and 473 mL Packets: 24 and 50s.	Apply to the affected area(s) of the skin two to four times a day as needed.
Tyzeka	Look/Sound	600 mg	600 mg by mouth daily
Tyzine	Look	Nasal solution: 0.1%, 0.05% Nasal spray: 0.1%	2-4 drops in each nostril every 3 hours
Zavesca	Look	100 mg	One capsule by mouth three times daily
Zycose	Look	1 mg/150 mg/850 mg	1 tablet twice daily

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