CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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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
Office of Medication Error Prevention and Risk Management

Proprietary Name Review

Date:	May 30, 2013
Reviewer:	Jung Lee, RPh Division of Medication Error Prevention and Analysis
Team Leader:	Jamie Wilkins Parker, PharmD Division of Medication Error Prevention and Analysis
Director:	Carol Holquist, RPh Division of Medication Error Prevention and Analysis
Drug Name and Strengths:	Astagraf XL (Tacrolimus Extended-release) Capsules, 0.5 mg, 1 mg, and 5 mg
Application Type/Number:	NDA 204096
Applicant:	Astellas Pharma, Inc
OSE RCM #:	2013-897

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

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1 INTRODUCTION

This review evaluates the proposed proprietary name, Astagraf XL, from a safety and promotional perspective. The sources and methods used to evaluate the proposed name are outlined in the reference section and Appendix A, respectively.

1.1 REGULATORY HISTORY

The proposed proprietary name, Astagraf XL, is the fifth name submitted for this product. The previous names reviewed include:

1. Prograf MR (OSE review # 06-0114, dated April 20, 2006)
2. Prograf XL (OSE review # 2006-143, dated September 7, 2006)
3. Advagraf (OSE review # 2007-2052, dated March 22, 2007 and OSE review #2012-1212 and #2012-2549 dated November 19, 2012)
4. Graceptor XL (OSE review # 2013-127, dated April 4, 2013).

On April 9, 2013, the Applicant submitted the Request for Proprietary Name Review for the proposed proprietary name Astagraf XL under NDA 204096.

1.2 PRODUCT INFORMATION

The following product information is provided in the April 9, 2013 proprietary name submission.

- Active Ingredient: Tacrolimus
- Indication of Use: Prophylaxis of organ rejection in adult patients receiving kidney transplants
- Route of Administration: Oral
- Dosage Form: Extended-Release Capsule
- Strength: 0.5 mg, 1 mg, and 5 mg
- Dose and Frequency: Once daily oral administration. The dosage of Astagraf XL should be titrated based on clinical assessments of rejection and tolerability. Careful and frequent monitoring of tacrolimus trough concentrations is recommended.

Table 1. Summary of Initial Oral Dosage Recommendations and Observed Whole Blood Trough Concentrations in Kidney Transplant Recipients

Patient Population	**Recommended Initial Once Daily (AM) Oral Dose**	**Observed Whole Blood Trough Concentrations**
Adult Kidney Transplant Patients	(b) (4) mg/kg/day	Day 1 to 60: 5-17 ng/mL Month 3-12: 4-12 ng/mL

Table 2. Astagraf XL Administration in Black Patients

Time After Transplant	White Patients n=160		Black Patients n=41	
	Dose (mg/kg)	Mean Trough Concentration (ng/mL)	Dose (mg/kg)	Mean Trough Concentration (ng/mL)
Day 7	0.14	10.65	0.14	7.78
Month 1	0.14	11.11	0.17	10.92
Month 6	0.10	7.95	0.13	8.42
Month 12	0.09	7.53	0.12	7.33

- How Supplied: 30-count bottles and 5 blister sheets of 10 capsules
- Storage: Store at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) (USP Controlled Room Temperature)
- Container and Closure System:
    - Bottles: A square high-density polyethylene (HDPE) bottle with a child resistant and tamper evident cap with a desiccant and a coil

STRENGTHS:	CAP COLORS:
0.5 mg	Brown
1 mg	Blue
5 mg	Orange

    - Blister Packs: Blister sheets wrapped in an (b) (4) pouch with a desiccant

2. RESULTS

The following sections provide the information obtained and considered in the overall evaluation of the proposed proprietary name.

2.1 PROMOTIONAL ASSESSMENT

The Office of Prescription Drug Promotion OPDP determined the proposed name is acceptable from a promotional perspective. DMEPA and the Division of Transplant and Ophthalmology Products concurred with the findings of OPDP's promotional assessment of the proposed name.

2.2 SAFETY ASSESSMENT

The following aspects were considered in the safety evaluation of the name.

2.2.1 United States Adopted Names (USAN) SEARCH

The March 26, 2013 search of the United States Adopted Name (USAN) stems did not identify that a USAN stem is present in the proposed proprietary name.

2.2.2 Components of the Proposed Proprietary Name

The proposed name, Astagraf XL, is comprised of two components: 1) the proposed root name, Astagraf, and 2) a modifier, XL. The root name contains the suffix 'graf' which could sound similar to 'graft.' 'Graft' is a term applied most commonly to skin, bone and vascular grafting as well as to other tissue grafts. The modifier 'XL' is added to the proprietary name to highlight the extended release properties of the proposed drug product. DMEPA previously recommended a modifier such as 'XL' be appended to the proprietary name to further reduce the potential for confusion with the immediate release tacrolimus products (OSE Reviews #2012-1212 and 2012-2549, dated November 19, 2012). The modifier 'XL' was previously evaluated and determined to be acceptable and conveys the once daily dosing for this product (OSE Review #2013-127, dated April 4, 2013).

2.2.3 FDA Name Simulation Studies

Seventy-eight practitioners participated in DMEPA's prescription studies. The interpretations did not overlap with any currently marketed products. Additionally, the interpretations did not appear to sound or look similar to any currently marketed products or products in the pipeline for approval. Forty-two participants correctly identified the name Astagraf XL. The majority of correct interpretations occurred in the written studies. Common misinterpretations of the prefix "Ast" in the written studies include 'Act,' 'Art,' or 'Sit'. The verbal study participants misinterpreted the prefix 'Ast' as 'Act,' 'Afst,' 'Aft,' 'Ase,' 'Asi,' or 'Assd.' Misinterpretations of the suffix 'graf' in the verbal and written studies include 'glaf,' 'graft,' or 'graph.' In addition, several participants omitted the modifier 'XL' from the root name (2 inpatient participants and 1 verbal participant). DMEPA considered the various misinterpretations of the name Astagraf XL in our analysis (see Appendix B). See Appendix C for the complete listing of interpretations from the verbal and written prescription studies.

2.2.4 Comments from Other Review Disciplines at Initial Review

OSE sent an email to the Division of Transplant and Ophthalmology Products (DTOP) on April 24, 2013 for any comments or concerns related to the proposed name, Astagraf XL, at the initial phase of the proprietary name review. Note, this email follows the April 23, 2013 midpoint review email to the Division (section 2.2.6). Due to the pending PDUFA date (July 21, 2013), DMEPA conducted a preliminary assessment of the name, Astagraf XL. As a result, the midpoint communication was sent to the Division prior to the OSE PM's initial email for comments from the Division. In response to the OSE, April 24, 2013 e-mail, the Division of Transplant and Ophthalmology Products (DTOP) did not forward any comments or concerns relating to the proposed name at the initial phase of the proprietary name review.

2.2.5 Failure Mode and Effects Analysis of Similar Names

Appendix B lists possible orthographic and phonetic misinterpretations of the letters appearing in the proposed proprietary name, Astagraf XL. Table 1 lists the names with orthographic, phonetic, or spelling similarity to the proposed proprietary name, Astagraf XL identified by the primary reviewer and the Expert Panel Discussion (EPD).

Table 1: Collective List of Potentially Similar Names (DMEPA, EPD)					
Look Similar					
Name	***Source***	***Name***	***Source***	***Name***	***Source***
Actagen	FDA	Antagon	FDA	Cetapred	FDA
Actifed	FDA	Antizol	FDA	Estraguard	FDA
Actigall	FDA	Arcalyst	FDA	Aubagio	FDA
Actonel	FDA	Astarga	FDA	Estrasorb	FDA
Afeditab CR	FDA	(b) (4)**	FDA	Estrogel	FDA
Altafrin	FDA	Astelin	FDA	Estroject LA	FDA
Altoprev	FDA	Astepro	FDA	Optivite P.M.T.	FDA
Ambifed	FDA	Astragalus	FDA	Osteo-fem	FDA
Androgel	FDA	Astramorph	FDA		
Sound Similar					
Name	***Source***	***Name***	***Source***	***Name***	***Source***
Lastacaft	FDA				
Look and Sound Similar					
Name	***Source***	***Name***	***Source***	***Name***	***Source***
Advagraf***	FDA	Astacran	FDA	Prograf XL	FDA
Prograf	FDA				

Our analysis of the 31 names contained in Table 1 considered the information obtained in the previous sections along with their product characteristics. We determined all 31 names will not pose a risk for confusion based on look and sound-alike similarity as described in Appendices D through E.

2.2.6 FMEA of Confusion within the Product Line Due to Shared "graf" Suffix

The proposed product, Astagraf XL (tacrolimus extended-release), is a product line extension of the currently marketed product, Prograf (tacrolimus immediate-release) capsules. These products share many similarities including the same active ingredient (tacrolimus), same dosage form (capsule), route of administration (oral), strengths

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(0.5 mg, 1 mg, 5 mg), similar indications for use, similar prescribers, as well as a similar patient population. However, Astagraf XL will be dosed once-daily as compared to twice-daily dosing for Prograf.

Due to the occurrence of medication errors in the EU between the immediate-release (Prograf) and extended-release product (Advagraf), we considered whether or not the suffix 'graf,' would create an additional source of similarity between the two products despite the different prefixes of each name. Based on the error data obtained from the EU, we determined the confusion between these products was not associated with the similarity of the proprietary names but rather with the similarity of their established names (tacrolimus). Products were prescribed using the INN (International Nonproprietary Name) without specifying the immediate-release or extended-release formulation. This accounted for the majority of errors reported in the UK. Thus, the shared 'graf' suffix will not likely contribute to an increased risk of error at the point of prescribing or transcription of a drug order.

Moreover, additional strategies to further distinguish the labels and labeling of these products are being implemented. The Applicant proposes to differentiate the appearance of Prograf and Astagraf XL's bottle shapes, bottle sizes, color schemes, as well as differentiating the appearance of their capsules. A communication plan including a Dear Healthcare Providers, Dear Pharmacists, and Dear Professional Societies Letters to inform of the risk of medication errors will also be implemented upon the product's approval. Lastly, a warning statement regarding medication errors reported between tacrolimus immediate-release and tacrolimus extended-release capsules will be added to the Warnings and Precaution section of the insert labeling for Astagraf XL. The additional education efforts will increase awareness to the new extended-release product and label/labeling revisions will help to distinguish them on a pharmacy shelf.

2.2.7 Communication of DMEPA's Analysis at Midpoint of Review

DMEPA communicated our findings to the Division of Transplant and Ophthalmology Products in an e-mail on April 23, 2013. At that time we also requested additional information or concerns that could inform our review. Per e-mail correspondence from the Division of Transplant and Ophthalmology Products on April 24, 2013, they stated no additional concerns with the proposed proprietary name, Astagraf XL.

3 CONCLUSIONS

The proposed proprietary name is acceptable from both a promotional and safety perspective.

If you have further questions or need clarifications, please contact Karen Townsend OSE project manager, at 301-796-5413.

3.1 COMMENTS TO THE APPLICANT

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

If any of the proposed product characteristics as stated in your April 9, 2013 submission are altered, the name must be resubmitted for review.

4 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. This database also lists the orphan drugs.

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

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

5. ***Division of Medication Errors Prevention and Analysis proprietary name 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. ***U.S. Patent and Trademark Office (http://www.uspto.gov)***

   USPTO provides information regarding patent and trademarks.

8. ***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.

9. ***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.

10. ***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.

11. ***Access Medicine (www.accessmedicine.com)***

    Access Medicine® from McGraw-Hill contains full-text information from approximately 60 titles; it includes tables and references. Among the titles are: Harrison's Principles of Internal Medicine, Basic & Clinical Pharmacology, and Goodman and Gilman's The Pharmacologic Basis of Therapeutics.

12. ***USAN Stems (http://www.ama-assn.org/ama/pub/about-ama/our-people/coalitions-consortiums/united-states-adopted-names-council/naming-guidelines/approved-stems.shtml)***

    USAN Stems List contains all the recognized USAN stems.

13. ***Red Book (www.thomsonhc.com/home/dispatch)***

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

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

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

15. ***Medical Abbreviations (www.medilexicon.com)***

    Medical Abbreviations dictionary contains commonly used medical abbreviations and their definitions.

16. ***CVS/Pharmacy (www.CVS.com)***

    This database contains commonly used over the counter products not usually identified in other databases.

17. ***Walgreens (www.walgreens.com)***

    This database contains commonly used over the counter products not usually identified in other databases.

18. ***Rx List (www.rxlist.com)***

    RxList is an online medical resource dedicated to offering detailed and current pharmaceutical information on brand and generic drugs.

19. ***Dogpile (www.dogpile.com)***

    Dogpile is a Metasearch engine that searches multiple search engines including Google, Yahoo! and Bing, and returns the most relevant results to the search.

20. ***Natural Standard (http://www.naturalstandard.com)***

    Natural Standard is a resource that aggregates and synthesizes data on complementary and alternative medicine.

APPENDICES

Appendix A

FDA's Proprietary Name Risk Assessment considers the promotional and safety aspects of a proposed proprietary name. The promotional review of the proposed name is conducted by OPDP. OPDP evaluates proposed proprietary names to determine if they are overly fanciful, so as to misleadingly imply unique effectiveness or composition, as well as to assess whether they contribute to overstatement of product efficacy, minimization of risk, broadening of product indications, or making of unsubstantiated superiority claims. OPDP provides their opinion to DMEPA for consideration in the overall acceptability of the proposed proprietary name.

The safety assessment is conducted by DMEPA. DMEPA staff search a standard set of databases and information sources to identify names that are similar in pronunciation, spelling, and orthographically similar when scripted to the proposed proprietary name. Additionally, we consider inclusion of USAN stems or other characteristics that when incorporated into a proprietary name may cause or contribute to medication errors (i.e., dosing interval, dosage form/route of administration, medical or product name abbreviations, names that include or suggest the composition of the drug product, etc.). 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]

Following the preliminary screening of the proposed proprietary name, DMEPA gathers to discuss their professional opinions on the safety of the proposed proprietary name. This meeting is commonly referred to the Center for Drug Evaluation and Research (CDER) Expert Panel discussion. DMEPA also considers other aspects of the name that may be misleading from a safety perspective. DMEPA staff conducts a prescription simulation studies using FDA health care professionals. When provided, DMEPA considers external proprietary name studies conducted by or for the Applicant/Sponsor and incorporates the findings of these studies into the overall risk assessment.

The DMEPA primary reviewer assigned to evaluate the proposed proprietary name 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 misleading nature of the proposed proprietary name with a focus on the avoidance of medication errors.

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. DMEPA considers the product characteristics associated with the proposed product 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.

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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.

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. DMEPA considers how these product characteristics may or may not be present in communicating a product name throughout the medication use system. Because drug name confusion can occur at any point in the medication use process, DMEPA 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.[2]

The DMEPA considers the spelling of the name, pronunciation of the name when spoken, and appearance of the name when scripted. DMEPA compares the proposed proprietary name with the proprietary and established name of existing and proposed drug products and names currently under review at the FDA. DMEPA 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. DMEPA examines the phonetic similarity using patterns of speech. If provided, DMEPA will consider the Sponsor's intended pronunciation of the proprietary name. However, DMEPA also considers a variety of pronunciations that could occur in the English language because the Sponsor has little control over how the name will be spoken in clinical practice. The orthographic appearance of the proposed name is evaluated using a number of different handwriting samples. DMEPA applies expertise gained from root-cause analysis of postmarketing 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).

[2] 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/Similar shape Upstrokes Down strokes Cross-strokes 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, DMEPA 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 searches 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. A standard description of the databases used in the searches is provided in the reference section of this review. To complement the process, the DMEPA uses 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, DMEPA reviews 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. DMEPA also evaluates if there are characteristics included in the composition that may render the name unacceptable from a safety perspective (abbreviation, dosing interval, etc.).

2. Expert Panel Discussion

DMEPA gathered CDER professional opinions on the safety of the proposed product and discussed the proposed proprietary name (Expert Panel Discussion). The Expert Panel is composed of Division of Medication Errors Prevention (DMEPA) staff and representatives from the Office of Prescription Drug Promotion (OPDP). We also consider input from other review disciplines (OND, ONDQA/OBP). 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 database and information searches to the Expert Panel for consideration. Based on the clinical and professional experiences of the Expert Panel members, the Panel may recommend additional 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 Simulation 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 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 record their interpretations of the orders which are recorded electronically.

4. Comments from Other Review Disciplines

DMEPA requests the Office of New Drugs (OND) and/or Office of Generic Drugs (OGD), ONDQA or OBP for their comments or concerns with the proposed proprietary name, ask for any clinical issues that may impact the DMEPA review during the initial phase of the name review. Additionally, when applicable, at the same time DMEPA requests concurrence/non-concurrence with OPDP's decision on the name. The primary Safety Evaluator addresses any comments or concerns in the safety evaluator's assessment.

The OND/OGD Regulatory Division is contacted a second time following our analysis of the proposed proprietary name. At this point, DMEPA conveys their decision to accept or reject the name. The OND or OGD Regulatory Division is requested to provide any further information that might inform DMEPA's final decision on the proposed name.

Additionally, other review disciplines opinions such as ONDQA or OBP may be considered depending on the proposed proprietary name.

5. Safety Evaluator Risk Assessment of the Proposed Proprietary Name

The primary Safety Evaluator applies his/her individual expertise gained from evaluating medication errors reported to FDA, considers all aspects of the name that may be misleading or confusing, conducts a Failure Mode and Effects Analysis, and provides an overall decision on acceptability dependent on their 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.[3] 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

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

characteristics listed in Section 1.2 of this review. 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? And are there any components of the name that may function as a source of error beyond sound/look-alike?"***

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 or because of some other component of the name. 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.

Moreover, 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 Overall Risk Assessment:

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

b. DMEPA identifies that the proposed proprietary name is misleading because of similarity in spelling or pronunciation to another proprietary or established name of a different drug or ingredient [CFR 201.10.(C)(5)].

c. FMEA identifies the potential for confusion between the proposed proprietary name and other proprietary or established drug name(s), and demonstrates that medication errors are likely to result from the drug name confusion under the conditions of usual clinical practice.

d. The proposed proprietary name contains an USAN (United States Adopted Names) stem.

e. DMEPA identifies a potential source of medication error within the proposed proprietary name. For example, the proprietary name may be misleading or, inadvertently, introduce ambiguity and confusion that leads to errors. Such errors may not necessarily involve confusion between the proposed drug and another drug product but involve a naming characteristic that when incorporated into a proprietary name, may be confusing, misleading, cause or contribute to medication errors.

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 generally recommends that the Sponsor select an alternative proprietary name and submit the alternate name to the Agency for 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 Sponsor 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/Sponsor. However, the safety concerns set forth in criteria a through e above are supported either by FDA regulation or by external healthcare authorities, including the Institute of Medicine (IOM), World Health Organization (WHO), the Joint Commission, and the Institute for Safe Medication Practices (ISMP). These organizations have examined medication errors resulting from look- or sound-alike drug names, confusing, or misleading 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 preventable source of medication error that, in many instances, the Agency and/or Sponsor 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. Sponsors have undertaken higher-leverage strategies, such as drug name changes, in the

past but at great financial cost to the Sponsor 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 Sponsors' 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.

Appendix B: Letters and Letter Strings with Possible Orthographic or Phonetic Misinterpretation

Letters in Name, Astagraf XL	Scripted May Appear as	Spoken May Be Interpreted as
Capital 'A'	ce, E, FL, H, s	Any vowel
Lower case 'a'	el, ci, cl, d, o, u	Any vowel
Lower case 's'	5, G, g, n, r	f, x, z
Lower case 't'	A, f, x, l	d
Lower case 'g'	j, q, s, y	c, k
Lower case 'r'	e, i, l, n, s, v	
Lower case 'f'	t	b, ph, s
Capital 'X'	d, f, K, P, t, U, V, Y	KS, KZ, S, Z
Lower case 'x'	a, d, skinny f, k, n, p, r, t, v, y	ks, kz, s, z
Capital 'L'	S, T, Z, d	w
Lower case 'l'	b, e, l, s, A, P	
Letter strings		
Ast	Act, Art, Aft, Cest, Cert, Cist, Cirt, Ost, Ort, Sit, Ust, Urt	Act, Afst, Aft, , Assd, Ase, Asi
ta	tra, te, ti, to, tu	ti, e, i, di
graf	giaf, geaf, giof, geof, geuf, giuf, yraf, yrof, yruf	glaf, graph, graft
XL		excel, SL

Appendix C: Prescription Simulation Samples and Results

Figure 1. Astagraf XL Study (Conducted on 3/7/13)

Handwritten Requisition Medication Order	Verbal Prescription
Medication Order: Astagraf XL 1mg po once daily Outpatient Prescription: Astagraf XL 0.5mg #30 1 po Qdaily	Astagraf XL 0.5 mg #30 Sig: 1 tablet po daily

FDA Prescription Simulation Responses (Aggregate 1 Rx Studies Report)

Study Name: Astagraf XL

As of Date 3/27/2013

191 People Received Study
78 People Responded

Total	26	23	29	78

INTERPRETATION	INPATIENT	VOICE	OUTPATIENT	TOTAL
ACTAGRAF XL	2	0	0	2
ACTIGRAF XL	0	1	0	1
ACTIGRAFT XL	0	1	0	1
ACTIGRAPH XL	0	4	0	4
AFSTIGRAPH	0	1	0	1
AFTAGRAF XL	0	1	0	1
AFTIGRAF XL	0	1	0	1
ARTAGRAF XL	2	0	0	2

ASEEGRAF XL	0	1	0	1
ASIGRAF XL	0	1	0	1
ASSDIGRAPH XL	0	1	0	1
ASTAGLAF	1	0	0	1
ASTAGLAF XL	1	0	0	1
ASTAGRAF	1	0	0	1
ASTAGRAF XL	15	2	24	41
ASTAGRAF XL 0.5MG	0	0	1	1
ASTAGRAFT XL	2	0	2	4
ASTAGRAPH XL	0	3	0	3
ASTIGRAF XL	0	5	0	5
ASTIGRAPH XL	0	1	0	1
ASTRAGRAF XL	0	0	2	2
ASTRAGRAPH XL	1	0	0	1
SITAGRAF XL	1	0	0	1

Appendix D: Proprietary names not likely to be confused or not used in usual practice settings for the reasons described. (n=14)

No.	Proprietary Name	Active Ingredient	Similarity to Astagraf XL	Failure preventions
1.	Actonel	Risedronate Sodium	Look Alike	The pair has sufficient orthographic differences
2.	Afeditab CR	Nifedipine	Look Alike	The pair has sufficient orthographic differences
3.	Altafrin	Phenylephrine HCl	Look Alike	The pair has sufficient orthographic differences
4.	Arcalyst	Rilonacept	Look Alike	The pair has sufficient orthographic differences
5.	Astarga	n/a	Look Alike	Name identified in USPTO. USPTO notes the status of this name as "Dead" as of May 19, 2005. Unable to find product characteristics in commonly used drug databases.
6.	(b) (4) ***	(b) (4)	Look Alike	The pair has sufficient orthographic differences
7.	Astelin	Azelastine HCl	Look Alike	The pair has sufficient orthographic differences
8.	Astragalus	Astragalus	Look Alike	The pair has sufficient orthographic differences
9.	Astramorph	Morphine Sulfate	Look Alike	The pair has sufficient orthographic differences
10.	Aubagio	Teriflunomide	Look Alike	The pair has sufficient orthographic differences
11.	Estraguard	Dienestrol	Look Alike	The pair has sufficient orthographic differences
12.	Optivite P.M.T.	Multivitamin	Look Alike	The pair has sufficient orthographic differences
13.	Osteo-fem	Multivitamin and Minerals	Look Alike	The pair has sufficient orthographic differences
14.	Astacran	Astaxanthin and Cranberry Seed Extract	Look and Sound Alike	The pair has sufficient orthographic and phonetic differences

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

Appendix E: Risk of medication errors due to product confusion minimized by dissimilarity of the names and/ or use in clinical practice for the reasons described. (n=17)

No.	**Proposed name:** Astagraf XL **Dosage Form:** Extended-Release Capsule **Strengths:** 0.5 mg, 1 mg, 5 mg **Usual Dose:** (b) (4)	**Failure Mode: Incorrect Product Ordered/ Selected/Dispensed or Administered because of Name confusion** **Causes (could be multiple)**	**Prevention of Failure Mode** **In the conditions outlined below, the following combination of factors, are expected to minimize the risk of confusion between these two names**
1.	Actagen (Triprolidine and Pseudoephedrine) Tablet **Strength:** 2.5 mg/60 mg **Usual Dose:** ½ to 1 tablet by mouth every 4 to 6 hours, no more than 4 doses in 24 hours	**Orthographic Similarity:** Both names begin with the identical letter 'A,' and contain the same letter string in the infix ('tag'). Route of Administration: Both are given orally. Dose: Dose overlap. Both may be written as 1 dose without specifying the dosage form (1 tablet vs. 1 capsule). In addition, a dose of 2.5 mg is achievable with both products.	**Orthographic Difference:** Astagraf contains an upstroke or downstroke 'f' in the last position of the name which is not seen in Actagen giving both names a different shape and appearance. **Differentiating Product Characteristics:** Strength: Astagraf XL is available in multiple strengths; therefore, a strength would need to be specified when prescribed on an order. Frequency: Every 4 to 6 hours vs. once daily

No.	**Proposed name:** Astagraf XL **Dosage Form:** Extended-Release Capsule **Strengths:** 0.5 mg, 1 mg, 5 mg **Usual Dose:** (b) (4)	**Failure Mode: Incorrect Product Ordered/ Selected/Dispensed or Administered because of Name confusion** **Causes (could be multiple)**	**Prevention of Failure Mode** **In the conditions outlined below, the following combination of factors, are expected to minimize the risk of confusion between these two names**
2.	Actifed (Phenylephrine HCl and Chlorpheniramine Maleate) Tablet **Strength:** 4 mg/10 mg **Usual Dose:** 1 tablet by mouth every 4 hours, up to 6 per day	**Orthographic Similarity:** Both names begin with the identical letter 'A,' contain a cross-stroke 't' in the 3rd position, a downstroke (f vs. g) in the 5th position, and an upstroke (d vs. f) in the last position of their names. Route of Administration: Both are given orally. Dose: Both may be written as 1 dose without specifying the dosage form (1 tablet vs. 1 capsule).	**Differentiating Product Characteristics:** Strength: No strength overlap. Astagraf XL is available in multiple strengths; therefore, a strength would need to be specified when prescribed on an order. Frequency: Every 4 hours vs. once daily

No.	**Proposed name:** Astagraf XL **Dosage Form:** Extended-Release Capsule **Strengths:** 0.5 mg, 1 mg, 5 mg **Usual Dose:** (b) (4)	**Failure Mode: Incorrect Product Ordered/ Selected/Dispensed or Administered because of Name confusion** **Causes (could be multiple)**	**Prevention of Failure Mode** **In the conditions outlined below, the following combination of factors, are expected to minimize the risk of confusion between these two names**
3.	Actigall (Ursodiol) Capsule **Strength:** 300 mg **Usual Dose:** 300 mg by mouth twice daily or 8 mg/kg/day to 10 mg/kg/day in 2 to 3 divided doses. For example, a patient weighing 75 kg would receive 600 mg to 750 mg daily.	**Orthographic Similarity:** Both names contain 8 letters, begin with the identical letter 'A,' contain a cross-stroke 't' in the 3rd position, a downstroke 'g' in the 5th position, and an upstroke (l vs. f) in the last position of their names. Dosage Form: Both are available as capsules. Route of Administration: Both are given orally. Dose: Both may be written as 1 or 2 capsules.	**Orthographic Difference:** Actigall contains an extra upstroke 'l' in the suffix of the name which is not seen in Astagraf giving both names a different shape and appearance. **Differentiating Product Characteristics:** Strength: Astagraf XL is available in multiple strengths; therefore, a strength would need to be specified when prescribed on an order. Frequency: Twice daily to three times daily vs. once daily

No.	**Proposed name:** Astagraf XL **Dosage Form:** Extended-Release Capsule **Strengths:** 0.5 mg, 1 mg, 5 mg **Usual Dose:** (b) (4)	**Failure Mode: Incorrect Product Ordered/ Selected/Dispensed or Administered because of Name confusion** **Causes (could be multiple)**	**Prevention of Failure Mode** **In the conditions outlined below, the following combination of factors, are expected to minimize the risk of confusion between these two names**
4.	Altoprev (Lovastatin) Extended-release Tablet **Strength:** 20 mg, 40 mg, 60 mg **Usual Dose:** 20 mg to 60 mg by mouth once daily	**Orthographic Similarity:** Both names contain 8 letters, begin with the identical letter 'A,' contain a cross-stroke 't' in the 3rd position of the name, and a downstroke (p vs. g) in the 5th position of their names. Route of Administration: Both are given orally. Dose: Both may be written as 1 dose without specifying the dosage form (1 tablet vs. 1 capsule). Frequency: Both could be prescribed as once daily.	**Orthographic Difference:** Altoprev contains an upstroke 'l' in the 2nd position of the name which is not seen in Astagraf, and Astagraf contains an upstroke or downstroke 'f' in the last position of the name which is not seen in Altoprev giving both names a different shape and appearance. **Differentiating Product Characteristics:** Strength: No strength overlap. Both Astagraf XL and Altoprev are available in multiple strengths; therefore, a strength would need to be specified for both drugs when prescribed on an order.

No.	Proposed name: Astagraf XL Dosage Form: Extended-Release Capsule Strengths: 0.5 mg, 1 mg, 5 mg Usual Dose: (b) (4)	Failure Mode: Incorrect Product Ordered/ Selected/Dispensed or Administered because of Name confusion Causes (could be multiple)	Prevention of Failure Mode In the conditions outlined below, the following combination of factors, are expected to minimize the risk of confusion between these two names
5.	Ambifed (Pseudoephedrine HCl and Guaifenesin) Tablet **Strength:** 30 mg/400 mg **Usual Dose:** ½ to 1 tablet by mouth every 4 to 6 hours, up to 6 tablets per 24 hours	**Orthographic Similarity:** Both names begin with the identical letter 'A', contain a downstroke (f vs. g) in the 5th position, and contain an upstroke in the 3rd and last position of their names. Route of Administration: Both are given orally. Dose: Both may be written as 1 dose without specifying the dosage form (1 tablet vs. 1 capsule).	**Orthographic Difference:** Astagraf contains the letters 'raf' in the suffix while Ambifed contains the letters 'ed' giving the suffix of Astagraf a longer appearance when scripted. **Differentiating Product Characteristics:** Strength: No strength overlap. Astagraf XL is available in multiple strengths; therefore, a strength would need to be specified when prescribed on an order. Frequency: Every 4 to 6 hours vs. once daily

No.	Proposed name: Astagraf XL Dosage Form: Extended-Release Capsule Strengths: 0.5 mg, 1 mg, 5 mg Usual Dose: (b) (4)	Failure Mode: Incorrect Product Ordered/ Selected/Dispensed or Administered because of Name confusion Causes (could be multiple)	Prevention of Failure Mode In the conditions outlined below, the following combination of factors, are expected to minimize the risk of confusion between these two names
6.	Androgel (Testosterone) Transdermal Gel Packets **Strengths:** 25 mg/2.5 gm, 50 mg/5 gm **Usual Dose:** 5 gm (50 mg) to 10 gm (100 mg) applied once daily in AM to shoulders and/or upper arms or abdomen Androgel Pump (Testosterone) Transdermal Gel **Strength:** 1.25 gm/Act (1%), 20.25 mg/Actuation (1.62%) **Usual Dose:** Apply 20.25 mg (1 pump) to 81 mg (4 pumps) topically once daily in the morning to the shoulders and upper arms	**Orthographic Similarity:** Both names contain 8 letters, begin with the letter 'A', contain an upstroke (d vs. t) in the 3rd position, a downstroke 'g' in the infix, and an upstroke at the end of their names (l vs. f). Dose: Numeric dose overlap (5 gm vs. 5 mg). Both may be written as 1 dose (1 pump vs. 1 capsule). Frequency: Both may be prescribed once daily.	**Orthographic Difference:** Androgel contains the letters 'ro' in the infix versus the letter 'a' in Astagraf giving the infix of Androgel a longer appearance. Also, Astagraf contains the letter string 'ra' in the suffix ('graf') vs. 'e' in Androgel ('gel') giving the suffix of Astagraf a longer appearance when scripted. **Differentiating Product Characteristics:** Strength and Dosage Form: No strength overlap. Both Astagraf XL and Androgel are available in multiple strengths and dosage forms; therefore, a strength and/or dosage form (Packet or Pump vs. Capsule) would need to be specified when prescribed on an order.

No.	**Proposed name:** Astagraf XL **Dosage Form:** Extended-Release Capsule **Strengths:** 0.5 mg, 1 mg, 5 mg **Usual Dose:** (b) (4)	**Failure Mode: Incorrect Product Ordered/ Selected/Dispensed or Administered because of Name confusion** **Causes (could be multiple)**	**Prevention of Failure Mode** **In the conditions outlined below, the following combination of factors, are expected to minimize the risk of confusion between these two names**
7.	Antagon (Ganirelix Acetate) Injection Solution **Strength:** 250 mcg/0.5 mL **Usual Dose:** After initiating follicle-stimulating hormone (FSH) therapy on day 2 or 3 of the cycle, administer 250 mcg (0.5 mL) subcutaneously once daily during the early to mid-follicular phase	**Orthographic Similarity:** Both names begin with the identical letter 'A,' contain a cross-stroke 't' in the 3rd position, and a downstroke 'g' in the 5th position of their names. Frequency: Both may be prescribed once daily.	**Orthographic Difference:** Astagraf contains an upstroke or downstroke 'f' in the last position of the name which is not seen in Antagon giving both names a different shape and appearance. In addition, Astagraf contains the letters 'raf' in the suffix of the name while Antagon contains the letter 'on' giving the suffix of Astagraf a longer appearance when scripted. **Differentiating Product Characteristics:** Strength: No strength overlap. Astagraf XL is available in multiple strengths; therefore, a strength would need to be specified when prescribed on an order.

No.	Proposed name: Astagraf XL Dosage Form: Extended-Release Capsule Strengths: 0.5 mg, 1 mg, 5 mg Usual Dose: (b) (4)	Failure Mode: Incorrect Product Ordered/ Selected/Dispensed or Administered because of Name confusion Causes (could be multiple)	Prevention of Failure Mode In the conditions outlined below, the following combination of factors, are expected to minimize the risk of confusion between these two names
8.	Antizol (Fomepizole) Injection Solution **Strength:** 1 g/mL **Usual Dose:** Administer a loading dose of 15 mg/kg as a slow intravenous infusion over 30 minutes, then 10 mg/kg every 12 hours for 4 doses, then 15 mg/kg every 12 hours until ethylene glycol or methanol concentrations are undetectable or have been reduced to less than 20 mg/dL, and the patient is asymptomatic with normal pH. For example, a patient weighing 75 kg would receive a dose of 750 mg (0.75 mL) to 1125 mg (1.125 g or 1.125 mL).	**Orthographic Similarity:** Both names begin with the identical letter 'A,' contain a cross-stroke 't' in the 3rd position, a downstroke (z vs. g) in the 5th position, and an upstroke (l vs. f) in the last position of their names.	**Orthographic Difference:** Astagraf contains the letters 'ra' in the suffix of the name while Antizol contains the letter 'o' giving the suffix of Astagraf a longer appearance when scripted. **Differentiating Product Characteristics:** Strength: Astagraf XL is available in multiple strengths; therefore, a strength would need to be specified when prescribed on an order. Frequency: Slow intravenous infusion over 30 minutes, then every 12 hours vs. once daily

No.	**Proposed name:** Astagraf XL **Dosage Form:** Extended-Release Capsule **Strengths:** 0.5 mg, 1 mg, 5 mg **Usual Dose:** (b) (4)	**Failure Mode: Incorrect Product Ordered/ Selected/Dispensed or Administered because of Name confusion** **Causes (could be multiple)**	**Prevention of Failure Mode** **In the conditions outlined below, the following combination of factors, are expected to minimize the risk of confusion between these two names**
9.	Astepro (Azelastine HCl) Nasal Solution **Strength:** 0.15% **Usual Dose:** 1 to 2 sprays per nostril twice daily or 2 sprays per nostril once daily	**Orthographic Similarity:** Both names begin with the identical letter string (Ast) and contain a downstroke (p vs. g) in the 5th position of their names. Dose: Both may be written as 1 or 2 doses without specifying the dosage form (2 sprays vs. 2 capsules). Frequency: Both may be prescribed once daily.	**Orthographic Difference:** Astagraf contains an upstroke or downstroke 'f' in the last position of the name which is not seen in Astepro giving both names a different shape and appearance. **Differentiating Product Characteristics:** Strength: No strength overlap. Astagraf XL is available in multiple strengths; therefore, a strength would need to be specified when prescribed on an order.

No.	**Proposed name:** Astagraf XL **Dosage Form:** Extended-Release Capsule **Strengths:** 0.5 mg, 1 mg, 5 mg **Usual Dose:** (b) (4)	**Failure Mode: Incorrect Product Ordered/ Selected/Dispensed or Administered because of Name confusion** **Causes (could be multiple)**	**Prevention of Failure Mode** **In the conditions outlined below, the following combination of factors, are expected to minimize the risk of confusion between these two names**
10.	Cetapred (Prednisolone Acetate and Sulfacetamide Sodium) Ophthalmic Ointment **Strength:** 0.25%/10% **Usual Dose:** Place a small amount (1/2 inch ribbon of ointment) into the affected eye(s) 3 or 4 times daily and once or twice at night.	**Orthographic Similarity:** Both names contain 8 letters, begin with orthographically similar letters (Ce vs. A), contain a cross-stroke 't' in the 3rd position, a downstroke (p vs. g) in the 5th position, and an upstroke (d vs. f) in the last position of their names.	**Orthographic Difference:** Astagraf contains the letter 's' before the cross-stroke 't' which is not seen in Cetapred giving the prefix of Astagraf a longer appearance. **Differentiating Product Characteristics:** Strength: No strength overlap. Astagraf XLis available in multiple strengths; therefore, a strength would need to be specified for Astagraf XL when prescribed on an order. Frequency: 3 or 4 times daily and once or twice at night vs. once daily

No.	Proposed name: Astagraf XL Dosage Form: Extended-Release Capsule Strengths: 0.5 mg, 1 mg, 5 mg Usual Dose: (b) (4)	Failure Mode: Incorrect Product Ordered/ Selected/Dispensed or Administered because of Name confusion Causes (could be multiple)	Prevention of Failure Mode In the conditions outlined below, the following combination of factors, are expected to minimize the risk of confusion between these two names
11.	Estrasorb (Estradiol Hemihydrate) Topical Emulsion **Strength:** 1.74 grams/packet **Usual Dose:** Apply 3.48 grams (two 1.74 gram pouches) daily	**Orthographic Similarity:** Both names begin with an orthographically similar letter string (Est vs. Ast) and end with an upstroke (b vs. f). Dose: Both may be written as 2 doses without specifying the dosage form (2 packets vs. 2 capsules). Frequency: Both may be prescribed once daily.	**Orthographic Difference:** Estrasorb contains the letters 'ra' following the cross-stroke 't' while Astagraf contains the letter 'a' giving the infix of Estrasorb a longer appearance when scripted. **Differentiating Product Characteristics:** Strength: No strength overlap. Astagraf XLis available in multiple strengths; therefore, a strength would need to be specified for Astagraf XL when prescribed on an order.

No.	Proposed name: Astagraf XL Dosage Form: Extended-Release Capsule Strengths: 0.5 mg, 1 mg, 5 mg Usual Dose: (b) (4)	Failure Mode: Incorrect Product Ordered/ Selected/Dispensed or Administered because of Name confusion Causes (could be multiple)	Prevention of Failure Mode In the conditions outlined below, the following combination of factors, are expected to minimize the risk of confusion between these two names
12.	Estrogel (Estradiol) Transdermal Gel **Strength:** 0.06% **Usual Dose:** 1.25 g once daily over entire area on the inside and outside of the arm from wrist to shoulder	**Orthographic Similarity:** Both names contain 8 letters, begin with an orthographically similar letter string (Est vs. Ast), and contain a downstroke 'g' in the infix, and contain an upstroke (l vs.f) in the last position of their names. Frequency: Both may be prescribed once daily. Dose: Both may be written as 1 dose without specifying the dosage form (1 pump vs. 1 capsule).	**Orthographic Difference:** Estrogel contains the letters 'ro' in the infix of the name while Astagraf contains the letter 'a' giving the infix of Estrogel a longer appearance. Also, Astagraf contains the letter string 'ra' in the suffix ('graf') vs. 'e' in Estrogel ('gel') giving the suffix of Astagraf a longer appearance when scripted. **Differentiating Product Characteristics:** Strength: No strength overlap. Astagraf XL is available in multiple strengths; therefore, a strength would need to be specified when prescribed on an order.

No.	Proposed name: Astagraf XL Dosage Form: Extended-Release Capsule Strengths: 0.5 mg, 1 mg, 5 mg Usual Dose: (b) (4)	Failure Mode: Incorrect Product Ordered/ Selected/Dispensed or Administered because of Name confusion Causes (could be multiple)	Prevention of Failure Mode In the conditions outlined below, the following combination of factors, are expected to minimize the risk of confusion between these two names
13.	Estroject LA (Estradiol Cypionate) Intramuscular Oil **Strength:** 5 mg/mL **Usual Dose:** 1.5 mg (0.3 mL) to 2 mg (0.4 mL) injected intramuscularly at monthly intervals or 1 mg (0.2 mL) to 5 mg (1 mL) intramuscularly every 3 to 4 weeks	**Orthographic Similarity:** Both names begin with an orthographically similar letter string (Est vs. Ast), contain a downstroke (j vs. g) in the infix, and contain an upstroke (t vs.f) in the last position of their names. Strength: Strength overlap (5 mg) Dose: Numeric dose overlap (5 mg (1 mL))	**Orthographic Difference:** Estroject contains the letters 'ro' in the infix of the name while Astagraf contains the letter 'a' giving the infix of Estroject a longer appearance. Also, the different modifiers (LA vs. XL) may help differentiate the names. **Differentiating Product Characteristics:** Frequency: Every 3 to 4 weeks vs. once daily

No.	Proposed name: Astagraf XL Dosage Form: Extended-Release Capsule Strengths: 0.5 mg, 1 mg, 5 mg Usual Dose: (b) (4)	Failure Mode: Incorrect Product Ordered/ Selected/Dispensed or Administered because of Name confusion Causes (could be multiple)	Prevention of Failure Mode In the conditions outlined below, the following combination of factors, are expected to minimize the risk of confusion between these two names
14.	Lastacaft (Alcaftadine) Ophthalmic Solution **Strength:** 0.25% **Usual Dose:** Instill 1 drop in each eye once daily	**Phonetic Similarity:** Both names contain 3 syllables in which the first 2 syllables sound similar when spoken ('Las'-'ta' vs. 'As'-'ta'). In addition, the last syllable in both names contains the letters 'af' which may sound similar when spoken. Frequency: Both may be prescribed once daily. Dose: Both may be written as 1 dose without specifying the dosage form (1 drop vs. 1 capsule).	**Differentiating Product Characteristics:** Strength: No strength overlap. Astagraf XLis available in multiple strengths; therefore, a strength would need to be specified for Astagraf XL when prescribed on an order

No.	Proposed name: Astagraf XL Dosage Form: Extended-Release Capsule Strengths: 0.5 mg, 1 mg, 5 mg Usual Dose: (b) (4)	Failure Mode: Incorrect Product Ordered/ Selected/Dispensed or Administered because of Name confusion Causes (could be multiple)	Prevention of Failure Mode In the conditions outlined below, the following combination of factors, are expected to minimize the risk of confusion between these two names
15	Advagraf (Tacrolimus Extended-release) Capsules Strengths: 0.5 mg, 1 mg, 5 mg Usual Dose: (b) (4)	Orthographic and Phonetic Similarities: Both names contain 8 letters, begin with the identical letter 'A,' and end with the same letter string 'agraf.' Both names contain 3 syllables in which the first letter 'A' and the last syllable in both names sound the same ('graf') when spoken.	Orthographic and Phonetic Differences: Advagraf contains an upstroke 'd' in the 2nd position of the name which is not seen in Astagraf. In addition, Astagraf contains a cross-stroke 't' in the 3rd position of the name which is not seen in Advagraf giving the prefix of both names a different shape and appearance when scripted. Also, the modifier 'XL' in Astagraf may help differentiate the names. When spoken, the first 2 syllables of both names sound different ('Ad'-'va' vs. 'As'-'ta').

No.	Proposed name: Astagraf XL Dosage Form: Extended-Release Capsule Strengths: 0.5 mg, 1 mg, 5 mg Usual Dose: (b) (4)	Failure Mode: Incorrect Product Ordered/ Selected/Dispensed or Administered because of Name confusion Causes (could be multiple)	Prevention of Failure Mode In the conditions outlined below, the following combination of factors, are expected to minimize the risk of confusion between these two names
16.	Prograf (Tacrolimus) Capsule **Strengths:** 0.5 mg, 1 mg, 5 mg **Usual Dose:** Heart Transplant: 0.75 mg/kg/day by mouth in 2 divided doses every 12 hours. For example, a patient weighing 75 kg would receive approximately 28 mg twice daily. Kidney Transplant: 0.2 mg/kg/day by mouth in combination with azathioprine or 0.1 mg/kg/day in combination with mycophenolate mofetil and interleukin-2 receptor antagonist every 12 hours. For example, a patient weighing 75 kg would receive 3.75	**Orthographic and Phonetic Similarities:** Both names end with the identical letter string 'graf'. When spoken, the last syllable in both names sound identical ('graf' vs. 'graf'). **Strength:** Strength overlap. Both products are available in 0.5 mg, 1 mg and 5 mg. **Dosage Form:** Both are capsules. **Route of Administration:** Both are given orally.	**Orthographic and Phonetic Differences:** The letter strings in the prefix of both names (Pro vs. Asta) are not orthographically similar. Also, Astagraf contains an upstroke 't' in the 3rd position which is not seen in Prograf giving the prefix of Astagraf a different shape and longer appearance when written. In addition, the modifier 'XL' in the name Astagraf will help further differentiate the name pair. Prograf contains 2 syllables vs. Astagraf contains 3 syllables. When spoken, the first 2 syllables in the name Astagraf sound distinctly different than the first syllable in Prograf ('As'-'ta' vs. Pro).

No.	Proposed name: Astagraf XL Dosage Form: Extended-Release Capsule Strengths: 0.5 mg, 1 mg, 5 mg Usual Dose: (b) (4)	Failure Mode: Incorrect Product Ordered/ Selected/Dispensed or Administered because of Name confusion Causes (could be multiple)	Prevention of Failure Mode In the conditions outlined below, the following combination of factors, are expected to minimize the risk of confusion between these two names
	mg to 7.5 mg twice daily. Liver Transplant: 0.1 mg/kg/day to 0.2 mg/kg/day by mouth every 12 hours. For example a child weighing 15 kg would receive 0.75 mg to 1.5 mg twice daily.		
17.	Prograf XL (Tacrolimus Extended-release) Capsules Strengths: 0.5 mg, 1 mg, 5 mg Usual Dose: (b) (4)	Orthographic and Phonetic Similarities: Both names end with the same letter string 'graf' and contain the same modifier 'XL.' When spoken, the last syllable and the modifier in both names sound identical ('graf'-'XL').	Orthographic and Phonetic Differences: Astagraf begins with an orthographically different letter (A vs. P) and contains a cross-stroke in the 3rd position of the name which is not seen in Prograf giving the prefix of both names a different shape and appearance when scripted (Pro vs. Asta). Astagraf contains 3 syllables versus 2 syllables in Prograf. When spoken, the 1st syllable in Prograf sound distinctly different than the 1st and 2nd syllables in Astagraf ('Pro' vs. 'As'-'ta').

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/s/

JUNG E LEE
05/30/2013

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05/30/2013

CAROL A HOLQUIST
05/31/2013

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Proprietary Name Review

Date:	April 4, 2013
Reviewer:	Jung Lee, RPh Division of Medication Error Prevention and Analysis
Team Leader:	Jamie Wilkins Parker, PharmD Division of Medication Error Prevention and Analysis
Deputy Director:	Kellie Taylor, PharmD, MPH Division of Medication Error Prevention and Analysis
Division Director:	Carol Holquist, RPh Division of Medication Error Prevention and Analysis
Drug Name and Strengths:	Graceptor XL (Tacrolimus Extended-release capsules), 0.5 mg, 1 mg, 5 mg
Application Type/Number:	NDA 204096
Applicant:	Astellas Pharma
OSE RCM #:	2013-127

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

CONTENTS

1 INTRODUCTION

This review evaluates the proposed proprietary name, Graceptor XL, from a safety and promotional perspective. The sources and methods used to evaluate the proposed name are outlined in the reference section and Appendix A respectively.

1.1 REGULATORY HISTORY

The proposed proprietary name, Graceptor XL, is the fourth name submitted for this product. The previous names reviewed include:

1. Prograf MR (OSE review #06-0114, dated April 20, 2006) found unacceptable by DMEPA due to the modifier "MR" which is not a USP recognized dosage form.
2. Prograf XL (OSE review #2006-143, dated September 7, 2006) initially found acceptable by DMEPA but later overturned by the Division of Transplants and Ophthalmology Products and found unacceptable. In the Division's preliminary responses to questions posted in the Applicant's briefing package dated March 20, 2007, the Division recommended that the Applicant not use Prograf XL and instead use the name Advagraf in order to harmonize the name internationally since it is marketed in Europe, and to minimize potential confusion between Prograf and Prograf XL.
3. Advagraf (OSE review #2007-2052, dated March 22, 2007) found acceptable by DMEPA, then found unacceptable from a promotional perspective in OSE review #2012-1212 and #2012-2549 dated November 19, 2012. DMEPA also found the name unacceptable from a medication safety perspective because the proposed name did not distinguish this extended-release product from the currently marketed immediate-release tacrolimus product due to the lack of a modifier to convey the product's extended-release properties.

On September 20, 2012, the Applicant submitted NDA 204096 with the indication for use in patients receiving kidney transplants and only male patients receiving liver transplants. The Applicant submitted the Request for Proprietary Name Review for the proposed proprietary name Graceptor XL on January 3, 2013. Graceptor XL is the proposed name for tacrolimus extended-release capsules. Tacrolimus is a macrolide immunosuppressant produced by Streptomyces tsukubaensis. On February 6, 2013, the Applicant withdrew the indication for liver transplants in male patients only.

1.2 PRODUCT INFORMATION

The following product information is provided in the March 14, 2013 package insert labeling submission.

- Active Ingredient: Tacrolimus
- Indication of Use: Prophylaxis of organ rejection in adult patients receiving kidney transplants
- Route of Administration: Oral
- Dosage Form: Extended-Release Capsule

- Strengths: 0.5 mg, 1 mg, 5 mg
- Dose and Frequency: Once daily oral administration. The dosage of Graceptor XL should be titrated based on clinical assessments of rejection and tolerability. Careful and frequent monitoring of tacrolimus trough concentrations is recommended. The recommended initial dose ranges from [redacted] (b) (4)

Table 1. Summary of Initial Oral Dosage Recommendations and Observed Whole Blood Trough Concentrations in Kidney Transplant Recipients

Patient Population	Recommended Initial Once Daily (AM) Oral Dose	Observed Whole Blood Trough Concentrations
Adult Kidney Transplant Patients	[redacted] (b) (4) mg/kg/day	Day 1 to 60: 5-17 ng/mL Month 3-12: 4-12 ng/mL

Table 2. Graceptor XL Administration in Black Patients

Time After Transplant	White Patients n=160		Black Patients n=41	
	Dose (mg/kg)	Mean Trough Concentration (ng/mL)	Dose (mg/kg)	Mean Trough Concentration (ng/mL)
Day 7	0.14	10.65	0.14	7.78
Month 1	0.14	11.11	0.17	10.92
Month 6	0.10	7.95	0.13	8.42
Month 12	0.09	7.53	0.12	7.33

- How Supplied: 30-count bottles and 5 blister sheets of 10 capsules
- Storage: Store at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) (USP Controlled Room Temperature)
- Container and Closure System:
  - Bottles: A square high-density polyethylene (HDPE) bottle with a child resistant and tamper evident cap with a desiccant and a coil

STRENGTHS:	CAP COLORS:
0.5 mg	Brown
1 mg	Blue
5 mg	Orange

  - Blister Packs: Blister sheets wrapped in an [redacted] (b) (4) pouch with a desiccant

2. RESULTS

The following sections provide the information obtained and considered in the overall evaluation of the proposed proprietary name.

2.1 PROMOTIONAL ASSESSMENT

The Office of Prescription Drug Promotion OPDP determined the proposed name is acceptable from a promotional perspective. DMEPA and the Division of Transplant and Ophthalmology Products concurred with the findings of OPDP's promotional assessment of the proposed name.

2.2 SAFETY ASSESSMENT

The following aspects were considered in the safety evaluation of the name.

2.2.1 United States Adopted Names (USAN) SEARCH

The February 19, 2013 search of the United States Adopted Name (USAN) stems identified the other strings "–ac" and "–cept" in the name Graceptor XL. However, neither letter string is used in the USAN stem position and thus acceptable.

2.2.2 Components of the Proposed Proprietary Name

This proprietary name is comprised of two components: 1) the proposed root name, Graceptor, and 2) a modifier, XL. The Applicant indicated in their submission that the proposed name, Graceptor XL, harmonizes the US proprietary name with the proprietary name Graceptor currently used by the Applicant in Japan for this product. In addition, the modifier 'XL' has been added to the proprietary name to highlight the extended release properties of the proposed drug product. DMEPA recommended to the Applicant in OSE Review # 2012-1212 and 2012-2549 on November 19, 2012 that a modifier such as 'XL' be appended to the proprietary name to highlight the extended-release properties of the proposed product to further reduce the potential for confusion with the immediate release tacrolimus products. We evaluated this modifier in section 2.1.6.1.

2.2.3 FDA Name Simulation Studies

Seventy-eight practitioners participated in DMEPA's prescription studies. The interpretations did not overlap with or appear or sound similar to any currently marketed products. Thirty participants correctly identified the name Graceptor XL. Four prescription participants omitted the modifier, one from the inpatient and outpatient studies and two from the verbal study. Of the outpatient participants who misinterpreted the name, the letter 'G' was mistaken for the letters 'S', 'Gra,' or 'Ge' and the last letter 'r' was misinterpreted as the letter 'l.' In the inpatient study, most participants misinterpreted the first letter 'r' with the letter 'i' and the suffix 'or' with 'ro.' The verbal prescription study showed misinterpretations of the letter 'G' as 'C' or 'T' and the modifier 'XL' as the letters 'XR' or 'Excel.' See Appendix C for the complete listing of interpretations from the verbal and written prescription studies.

2.2.4 Comments from Other Review Disciplines

In response to the OSE, February 4, 2013 e-mail, the Division of Transplant and Ophthalmology Products (DTOP) did not forward any comments or concerns relating to the proposed name at the initial phase of the proprietary name review.

2.2.5 Failure Mode and Effects Analysis of Similar Names

Appendix B lists possible orthographic and phonetic misinterpretations of the letters appearing in the proposed proprietary name, Graceptor XL. Table 1 lists the names with orthographic, phonetic, or spelling similarity to the proposed proprietary name, Graceptor XL identified by the primary reviewer, the Expert Panel Discussion (EPD), and other review disciplines. Table 1 also includes the names identified by the Drug Safety Institute (DSI), not identified by DMEPA, and require further evaluation.

Table 1: Collective List of Potentially Similar Names (DMEPA, EPD, and External Name Study)

Look Similar					
Name	***Source***	***Name***	***Source***	***Name***	***Source***
Arcapta Neohaler	FDA	Genoptic Genoptic SOP	FDA	Graviola	FDA
Aricept XR***	FDA	Gilenya	DSI	Grisactin	FDA
Concept OB	FDA	Glucophage XR	FDA	Griseofulvin	DSI
Conceptrol	FDA	Glucotrol XL	FDA	Herceptin	FDA
Concerta	FDA	Grafco	DSI	Neurontin	DSI
Cresylate	FDA	Granisetron	FDA	Trancopal	FDA
Gencept 10/11	FDA	Granulex	FDA	Travoprost	FDA
Sound Similar					
Name	***Source***	***Name***	***Source***	***Name***	***Source***
Aventyl	DSI	Desvenlafaxine	DSI	Sinequan	DSI
Cellcept	DSI	Effexor	DSI		

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

Table 1: Collective List of Potentially Similar Names (DMEPA, EPD, and External Name Study)					
Look and Sound Similar					
Name	***Source***	***Name***	***Source***	***Name***	***Source***
Crestor	FDA	Genaspor	DSI	Rescriptor	FDA/DSI
Duloxetine	DSI	Graceptor	FDA	Trecator	DSI
Gabapentin	FDA/DSI	Gralise	DSI	Venlafaxine	DSI
Gamimune N	DSI	Granisol	FDA/DSI		
Gamunex	DSI	Lipitor	DSI		

Our analysis of the 39 names contained in Table 1 considered the information obtained in the previous sections along with their product characteristics. We determined 38 of the 39 total names will not pose a risk for confusion as described in Appendices D through E. However, the proposed name could be confused with Glucotrol XL. The rationale for the risk of confusion is described in Section 3.1.

2.2.6 Failure Mode and Effects Analysis of the Modifier XL

The proposed product, Graceptor XL, is an extended-release capsule to be administered once daily. The active ingredient, tacrolimus, is currently marketed as an immediate-release capsule by the same Applicant, Astellas, under the proprietary name Prograf. There are also generic immediate-release tacrolimus capsules marketed under the established name, tacrolimus.

Both Graceptor XL (tacrolimus extended-release) and the currently marketed tacrolimus immediate-release capsules have overlapping product characteristics including overlapping strengths (0.5 mg, 1 mg, and 5 mg), the same active ingredient (tacrolimus), and the same dosage form (capsule). However, Graceptor XL is an extended-release capsule that is administered once daily while tacrolimus immediate-release capsules are usually dosed twice daily but can also be dosed once daily, if dosage adjustment is needed.

Foreign post marketing data has shown medication errors reported between the two products due to confusion between the immediate-release and extended-release formulations and their dosing frequencies. Due to the products' overlapping product characteristics and different dosing frequencies, medication errors including incorrect frequency of dosing, inadvertent, unintentional or unsupervised substitution of one formulation for the other, and coadministration of the two formulations have led to overdosing and underdosing of tacrolimus and serious adverse events, including graft rejection.

For the aforementioned reasons, we determined in the previous name review (OSE Review # 2012-1212 and 2012-2549) that a modifier was necessary to distinguish this extended-release product from the immediate-release product.

The Applicant proposes the modifier 'XL' to signal the extended-release properties of their drug. There is no drug product currently marketed in the US named Graceptor. Thus, the use of a modifier is not necessarily needed to distinguish this product from a currently marketed "Graceptor" product. However, the use of the modifier 'XL' may inform healthcare providers that this new tacrolimus product is not an immediate-release formulation intended for twice daily administration.

Our evaluation of the modifier 'XL' has however identified it as a source of confusion when used with the product Procardia (Nifedipine). Orders for Procardia XL were mistakenly interpreted as "Procardia SL," and immediate-release nifedipine was consequently administered sublingually. The similarity of the 'XL' modifier to the abbreviation 'SL' for the sublingual route of administration, as well as the practitioners' knowledge regarding the use of nifedipine sublingually for the off-label management of stroke and pre-eclampsia, may have predisposed the clinician to confirmation bias when presented with the order for Procardia XL. In other words, their familiarity with sublingual use of nifedipine combined with the similarity of the modifier 'XL' to the abbreviation 'SL' led the practitioner to misinterpret the order. The risk of maladministration errors posed by the 'XL' modifier were not considered or evaluated as part of our Prograf XL review (OSE Review # 2006-143, dated 9/7/2006); however, for this particular product, tacrolimus, we are not aware of any labeled or off-label use that includes sublingual administration of the drug in the usual practice setting. Furthermore, none of the participants in our prescription studies misinterpreted 'XL' as 'SL.' Therefore, we conclude that although 'XL' is similar to 'SL,' the risk of misinterpreting the modifier as SL/sublingual administration is likely to be less with this tacrolimus product compared to other drugs that are routinely administered sublingually such as nifedipine.

With respect to signaling that the frequency of administration of this product (once daily) differs from immediate-release tacrolimus (twice daily), we find that the modifier 'XL' has only been used to communicate once daily dosing (e.g. Biaxin XL, Lescol XL, Glucotrol XL). Other modifiers for non immediate-release formulations such as 'CR,' 'SR,' 'CD,' etc. are associated with varied dosing frequencies from once to three times daily. Therefore the use of the modifier 'XL' is consistent with the dosing frequency of this product.

Although there has been misinterpretation of the modifier 'XL' for the route of administration abbreviation 'SL' for sublingual, it was in the context of use with a product that has appropriate and well-known sublingual administration, whereas this product does not have the same clinical use at this time. The modifier 'XL' also consistently conveys once daily dosing as evidenced by the currently marketed products bearing this modifier in the proprietary name. Therefore, we find the use of the modifier 'XL' to be appropriate for this product.

2.2.7 Communication of DMEPA's Final Decision to Other Disciplines

DMEPA communicated our findings to the Division of Transplant and Ophthalmology Products via e-mail on March 4, 2013. At that time we also requested additional information or concerns that could inform our review. Per e-mail correspondence from the Division of Transplant and Ophthalmology Products on March 8, 2013, they stated no additional concerns with the proposed proprietary name, Graceptor XL.

3 CONCLUSIONS

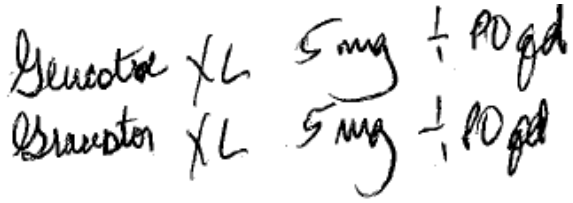
The proposed proprietary name is acceptable from a promotional perspective but not acceptable from a safety perspective. The proposed name is vulnerable to name confusion with the marketed product, Glucotrol XL. Therefore, the decision to deny the name will be communicated to the Applicant via letter (See Section 3.1).

If you have further questions or need clarifications, please contact Karen Townsend, OSE project manager, at 301-796-5413.

3.1 COMMENTS TO THE APPLICANT

We have completed our review of the proposed proprietary name, Graceptor XL, and have concluded that this name is unacceptable for the following reasons:

The proposed proprietary name, Graceptor XL, is orthographically similar to and has overlapping product characteristics with the currently marketed product, Glucotrol XL (Glipizide Extended-release) Tablets. Both names contain the same number of letters (9), begin with the letter 'G,' contain the letter 'c' in the 4th position, contain a cross-stroke 't' in a similar position which is closely followed by the letter 'o,' and both names have the same modifier 'XL.' Moreover, if both letters 'l' in Glucotrol are scripted without a prominent upstroke, the letters 'l' in Glucotrol may look similar to the letters 'r' in Graceptor. This similarity was confirmed by the Agency's prescription studies. Additionally, if the letter 'p' in Graceptor is scripted without a prominent downstroke, the infix letter string 'cep' in Graceptor may look similar to the letter string 'co' in Glucotrol. (See example below.)



In addition to the orthographic similarity of this name pair, the products have overlapping product characteristics such as strength (5 mg), dosage (2.5 mg, 5 mg, 10 mg), both are a solid oral dosage form, route of administration (oral), and frequency of administration (once daily). These overlapping product characteristics in conjunction with the orthographic similarity make the name pair vulnerable to confusion which can lead to wrong drug errors.

We acknowledge that our conclusion on the acceptability of the name differs from the conclusions reached by the Drug Safety Institute. However, the name Glucotrol XL was

not identified or evaluated in the external name review. There is no information provided in the submission that account for why the external consultants did not identify the name.

4 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. This database also lists the orphan drugs.

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

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

5. ***Division of Medication Errors Prevention and Analysis proprietary name 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. ***U.S. Patent and Trademark Office (http://www.uspto.gov)***

   USPTO provides information regarding patent and trademarks.

8. ***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.

9. ***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.

10. ***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.

11. ***Access Medicine (www.accessmedicine.com)***

    Access Medicine® from McGraw-Hill contains full-text information from approximately 60 titles; it includes tables and references. Among the titles are: Harrison's Principles of Internal Medicine, Basic & Clinical Pharmacology, and Goodman and Gilman's The Pharmacologic Basis of Therapeutics.

12. ***USAN Stems (http://www.ama-assn.org/ama/pub/about-ama/our-people/coalitions-consortiums/united-states-adopted-names-council/naming-guidelines/approved-stems.shtml)***

    USAN Stems List contains all the recognized USAN stems.

13. ***Red Book (www.thomsonhc.com/home/dispatch)***

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

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

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

15. ***Medical Abbreviations (www.medilexicon.com)***

    Medical Abbreviations dictionary contains commonly used medical abbreviations and their definitions.

16. ***CVS/Pharmacy (www.CVS.com)***

    This database contains commonly used over the counter products not usually identified in other databases.

17. ***Walgreens (www.walgreens.com)***

    This database contains commonly used over the counter products not usually identified in other databases.

18. ***Rx List (www.rxlist.com)***

    RxList is an online medical resource dedicated to offering detailed and current pharmaceutical information on brand and generic drugs.

19. ***Dogpile (www.dogpile.com)***

    Dogpile is a Metasearch engine that searches multiple search engines including Google, Yahoo! and Bing, and returns the most relevant results to the search.

20. ***Natural Standard (http://www.naturalstandard.com)***

    Natural Standard is a resource that aggregates and synthesizes data on complementary and alternative medicine.

APPENDICES

Appendix A

FDA's Proprietary Name Risk Assessment considers the promotional and safety aspects of a proposed proprietary name. The promotional review of the proposed name is conducted by OPDP. OPDP evaluates proposed proprietary names to determine if they are overly fanciful, so as to misleadingly imply unique effectiveness or composition, as well as to assess whether they contribute to overstatement of product efficacy, minimization of risk, broadening of product indications, or making of unsubstantiated superiority claims. OPDP provides their opinion to DMEPA for consideration in the overall acceptability of the proposed proprietary name.

The safety assessment is conducted by DMEPA. DMEPA staff search a standard set of databases and information sources to identify names that are similar in pronunciation, spelling, and orthographically similar when scripted to the proposed proprietary name. Additionally, we consider inclusion of USAN stems or other characteristics that when incorporated into a proprietary name may cause or contribute to medication errors (i.e., dosing interval, dosage form/route of administration, medical or product name abbreviations, names that include or suggest the composition of the drug product, etc.). 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]

Following the preliminary screening of the proposed proprietary name, DMEPA gathers to discuss their professional opinions on the safety of the proposed proprietary name. This meeting is commonly referred to the Center for Drug Evaluation and Research (CDER) Expert Panel discussion. DMEPA also considers other aspects of the name that may be misleading from a safety perspective. DMEPA staff conducts a prescription simulation studies using FDA health care professionals. When provided, DMEPA considers external proprietary name studies conducted by or for the Applicant/Sponsor and incorporates the findings of these studies into the overall risk assessment.

The DMEPA primary reviewer assigned to evaluate the proposed proprietary name 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 misleading nature of the proposed proprietary name with a focus on the avoidance of medication errors.

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. DMEPA considers the product characteristics associated with the proposed product 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.

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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.

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. DMEPA considers how these product characteristics may or may not be present in communicating a product name throughout the medication use system. Because drug name confusion can occur at any point in the medication use process, DMEPA 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.[2]

The DMEPA considers the spelling of the name, pronunciation of the name when spoken, and appearance of the name when scripted. DMEPA compares the proposed proprietary name with the proprietary and established name of existing and proposed drug products and names currently under review at the FDA. DMEPA 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. DMEPA examines the phonetic similarity using patterns of speech. If provided, DMEPA will consider the Sponsor's intended pronunciation of the proprietary name. However, DMEPA also considers a variety of pronunciations that could occur in the English language because the Sponsor has little control over how the name will be spoken in clinical practice. The orthographic appearance of the proposed name is evaluated using a number of different handwriting samples. DMEPA applies expertise gained from root-cause analysis of post marketing 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).

[2] 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/Similar shape Upstrokes Down strokes Cross-strokes 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, DMEPA 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 searches 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. A standard description of the databases used in the searches is provided in the reference section of this review. To complement the process, the DMEPA uses 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, DMEPA reviews 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. DMEPA also evaluates if there are characteristics included in the composition that may render the name unacceptable from a safety perspective (abbreviation, dosing interval, etc.).

2. Expert Panel Discussion

DMEPA gathered CDER professional opinions on the safety of the proposed product and discussed the proposed proprietary name (Expert Panel Discussion). The Expert Panel is composed of Division of Medication Errors Prevention (DMEPA) staff and representatives from the Office of Prescription Drug Promotion (OPDP). We also consider input from other review disciplines (OND, ONDQA/OBP). 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 database and information searches to the Expert Panel for consideration. Based on the clinical and professional experiences of the Expert Panel members, the Panel may recommend additional 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 Simulation 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 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 record their interpretations of the orders which are recorded electronically.

4. Comments from Other Review Disciplines

DMEPA requests the Office of New Drugs (OND) and/or Office of Generic Drugs (OGD), ONDQA or OBP for their comments or concerns with the proposed proprietary name, ask for any clinical issues that may impact the DMEPA review during the initial phase of the name review. Additionally, when applicable, at the same time DMEPA requests concurrence/non-concurrence with OPDP's decision on the name. The primary Safety Evaluator addresses any comments or concerns in the safety evaluator's assessment.

The OND/OGD Regulatory Division is contacted a second time following our analysis of the proposed proprietary name. At this point, DMEPA conveys their decision to accept or reject the name. The OND or OGD Regulatory Division is requested to provide any further information that might inform DMEPA's final decision on the proposed name.

Additionally, other review disciplines opinions such as ONDQA or OBP may be considered depending on the proposed proprietary name.

5. Safety Evaluator Risk Assessment of the Proposed Proprietary Name

The primary Safety Evaluator applies his/her individual expertise gained from evaluating medication errors reported to FDA, considers all aspects of the name that may be misleading or confusing, conducts a Failure Mode and Effects Analysis, and provides an overall decision on acceptability dependent on their 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.[3] 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

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

characteristics listed in Section 1.2 of this review. 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? And are there any components of the name that may function as a source of error beyond sound/look-alike?"***

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 or because of some other component of the name. 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.

Moreover, 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 Overall Risk Assessment:

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

b. DMEPA identifies that the proposed proprietary name is misleading because of similarity in spelling or pronunciation to another proprietary or established name of a different drug or ingredient [CFR 201.10.(C)(5)].

c. FMEA identifies the potential for confusion between the proposed proprietary name and other proprietary or established drug name(s), and demonstrates that medication errors are likely to result from the drug name confusion under the conditions of usual clinical practice.

d. The proposed proprietary name contains an USAN (United States Adopted Names) stem.

e. DMEPA identifies a potential source of medication error within the proposed proprietary name. For example, the proprietary name may be misleading or, inadvertently, introduce ambiguity and confusion that leads to errors. Such errors may not necessarily involve confusion between the proposed drug and another drug product but involve a naming characteristic that when incorporated into a proprietary name, may be confusing, misleading, cause or contribute to medication errors.

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 generally recommends that the Sponsor select an alternative proprietary name and submit the alternate name to the Agency for 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 Sponsor 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/Sponsor. However, the safety concerns set forth in criteria a through e above are supported either by FDA regulation or by external healthcare authorities, including the Institute of Medicine (IOM), World Health Organization (WHO), the Joint Commission, and the Institute for Safe Medication Practices (ISMP). These organizations have examined medication errors resulting from look- or sound-alike drug names, confusing, or misleading 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 preventable source of medication error that, in many instances, the Agency and/or Sponsor 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. Sponsors have undertaken higher-leverage strategies, such as drug name changes, in the

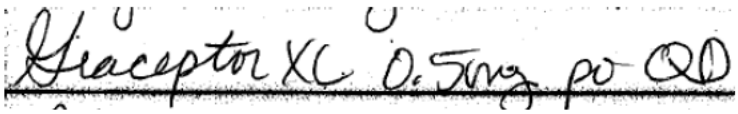
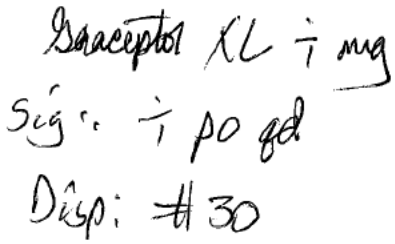
past but at great financial cost to the Sponsor and at the expense of the public welfare, not to mention the Agency's credibility as the authority responsible for approving the error-prone proprietary name. Moreover, even after Sponsors' have changed a product's proprietary name in the post-approval 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.

Appendix B: Letters and Letter Strings with Possible Orthographic or Phonetic Misinterpretation

Letters in Name, Graceptor XL	Scripted May Appear as	Spoken May Be Interpreted as
Capital 'G'	A, C, D, H, O, S, T	J
Lower case 'g'	j, q, s	k, j
Lower case 'r'	e, i, l, n, s, v	
Lower case 'a'	el, ci, cl, d, o, u	Any vowel
Lower case 'c'	a, e, i, l	z, s
Lower case 'e'	a, i, l, p	Any vowel
Lower case 'p'	g, j, l, q, yn, ys	B
Lower case 't'	A, f, x, l	D
Lower case 'o'	a, c, e, u	Oh
Lower case 'r'	e, i, l, n, s, v	
Capital 'X'	d, f, K, P, t, U, V, Y	KS, KZ, S, Z
Lower case 'x'	a, d, skinny f, k, n, p, r, t, v, y	ks, kz, s, z
Capital 'L'	S, T, Z, d	W
Lower case 'l'	b, e, l, s, A, P	
Letter strings		
Gra	Cra, Cre, Sra, Sre, Gara, Gera, Gia	Cra, Cre, Sra, Sre, Grep, Grese, Gre, Gres, Gri, Tri
cep	cys	sep, zep, seb, zeb, set, zet
tor	trol, tol	ter, tar, tro,
XL	LX	XR, Excel, SL

Appendix C: Prescription Simulation Samples and Results

Figure 1. Graceptor XL Study (Conducted on January 17, 2013)

Handwritten Requisition Medication Order	Verbal Prescription
Medication Order: 	Graceptor XL 1 mg #30 Sig: 1 po QD
Outpatient Prescription: 	

FDA Prescription Simulation Responses (Aggregate 1 Rx Studies Report)

				192 People Received Study 78 People Responded
Study Name: Graceptor XL				
Total	**30**	**25**	**23**	**78**
INTERPRETATION	**INPATIENT**	**VOICE**	**OUTPATIENT**	**TOTAL**
?	0	1	0	1
? XL	0	1	0	1
CRECEPTOR XL	0	2	0	2
CRESAPTOR XR	0	1	0	1
CRESCEPTOR XL	0	1	0	1
CRESEPTOR XL	0	1	0	1
GARACEPTOR XL	0	0	1	1
GERACEPTOR XL	0	0	1	1

GIACEPTOR XL	15	0	0	15
GIACEPTRO XL	1	0	0	1
GRACEPTOL	0	0	1	1
GRACEPTOL LX	0	0	1	1
GRACEPTOL XL	0	0	5	5
GRACEPTOR	1	1	0	2
GRACEPTOR XL	13	4	13	30
GRACEPTOR XR	0	1	0	1
GRASEPTER EXCEL	0	1	0	1
GRECEPTOR XL	0	3	0	3
GREPCEPTOR XL	0	1	0	1
GRESECEPTOR XL	0	1	0	1
GRESEPTOR XL	0	2	0	2
GRESSEPTOR XL	0	1	0	1
GREXEPTOR XL	0	1	0	1
GRICEPTAR	0	1	0	1
SRACEPTOR XL	0	0	1	1
TRICEPTRO XL	0	1	0	1

Appendix D: Proprietary names not likely to be confused or not used in usual practice settings for the reasons described. (n=27)

No.	Proprietary Name	Active Ingredient	Similarity to Graceptor XL	Failure preventions
1.	Aricept XR***	Donepezil HCl	Look Alike	Name originally found acceptable on April 6, 2010 (OSE Review #2009-2411) but later found unacceptable on May 24, 2010, following a teleconference with the Applicant on May 14, 2010, due to the determination that the product does not meet the criteria for an extended release formulation. Marketed under the existing name, Aricept.
2.	Concerta	Methylphenidate HCl	Look Alike	The pair has sufficient orthographic differences
3.	Cresylate	Cresylate	Look Alike	The pair has sufficient orthographic differences
4.	Gilenya	Fingolimod HCl	Look Alike	The pair has sufficient orthographic differences
5.	Glucophage XR	Metformin HCl	Look Alike	The pair has sufficient orthographic differences
6.	Grafco	Silver Nitrate, Potassium Nitrate	Look Alike	The pair has sufficient orthographic differences
7.	Granisetron	Granisetron HCl	Look Alike	The pair has sufficient orthographic differences
8.	Granulex	Trypsin, balsam peru, caster oil	Look Alike	The pair has sufficient orthographic differences
9.	Graviola	Graviola (Botanical Product)	Look Alike	The pair has sufficient orthographic differences
10.	Griseofulvin	Griseofulvin	Look Alike	The pair has sufficient orthographic differences
11.	Neurontin	Gabapentin	Look Alike	The pair has sufficient orthographic differences
12.	Trancopal	Chlormezanone	Look Alike	The pair has sufficient orthographic differences

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

No.	Proprietary Name	Active Ingredient	Similarity to Graceptor XL	Failure preventions
13.	Travoprost	Travoprost	Look Alike	The pair has sufficient orthographic differences
14.	Aventyl	Nortriptyline HCl	Sound Alike	The pair has sufficient orthographic and phonetic differences
15.	Cellcept	Mycophenolate Mofetil	Sound Alike	The pair has sufficient phonetic differences
16.	Desvenlafaxine	Desvenlafaxine Succinate	Sound Alike	The pair has sufficient phonetic differences
17.	Sinequan	Doxepin HCl	Sound Alike	The pair has sufficient phonetic differences
18.	Duloxetine	Duloxetine HCl	Look and Sound Alike	The pair has sufficient orthographic and phonetic differences
19.	Gabapentin	Gabapentin	Look and Sound Alike	The pair has sufficient orthographic and phonetic differences
20.	Gamimune N	Immune Globulin (Human)	Look and Sound Alike	The pair has sufficient orthographic and phonetic differences
21.	Gamunex	Immune Globulin (Human)	Look and Sound Alike	The pair has sufficient orthographic and phonetic differences
22.	Graceptor	Tacrolimus Extended-release	Look and Sound Alike	Atellas Pharma's international name for tacrolimus extended-release capsule in Japan.
23.	Gralise	Gabapentin	Look and Sound Alike	The pair has sufficient orthographic and phonetic differences
24.	Granisol	Granisetron HCl	Look and Sound Alike	The pair has sufficient orthographic and phonetic differences
25.	Lipitor	Atorvastatin Calcium	Look and Sound Alike	The pair has sufficient orthographic and phonetic differences
26.	Trecator	Ethionamide	Look and Sound Alike	The pair has sufficient orthographic and phonetic differences

No.	Proprietary Name	Active Ingredient	Similarity to Graceptor XL	Failure preventions
27.	Venlafaxine	Venlafaxine HCl	Look and Sound Alike	The pair has sufficient orthographic and phonetic differences

Appendix E: Risk of medication errors due to product confusion minimized by dissimilarity of the names and/ or use in clinical practice for the reasons described. (n=11)

No.	**Proposed name:** Graceptor XL **Dosage Form:** Extended-Release Capsule **Strengths:** 0.5 mg, 1 mg, 5 mg **Usual Dose:** (b) (4)	**Failure Mode: Incorrect Product Ordered/ Selected/Dispensed or Administered because of Name confusion** **Causes (could be multiple)**	**Prevention of Failure Mode** **In the conditions outlined below, the following combination of factors, are expected to minimize the risk of confusion between these two names**
1.	Arcapta Neohaler (Indacaterol) Inhalation Capsule **Strength:** 75 mcg **Usual Dose:** Inhale one capsule by mouth once daily	**Orthographic Similarity:** Both names contain orthographically similar letter strings (Gr vs. Ar) in the prefix and in the infix/suffix (cepto vs. capta). Dosage Form: Both are capsules. Frequency: Both could be prescribed as once daily. Dose: Both could be prescribed as one dose.	**Orthographic Difference:** When included, the modifier "Neohaler" would add additional distinction to the name Arcapta over the name Graceptor XL. **Differentiating Product Characteristics:** Strength: No strength overlap. Graceptor XL is available in multiple strengths; therefore, a strength would need to be specified when prescribed on an order.

No.	Proposed name: Graceptor XL Dosage Form: Extended-Release Capsule Strengths: 0.5 mg, 1 mg, 5 mg Usual Dose: (b) (4)	Failure Mode: Incorrect Product Ordered/ Selected/Dispensed or Administered because of Name confusion Causes (could be multiple)	Prevention of Failure Mode In the conditions outlined below, the following combination of factors, are expected to minimize the risk of confusion between these two names
2.	Concept OB (Prenatal Multivitamin) Capsule **Strength:** n/a **Usual Dose:** One capsule by mouth once daily	**Orthographic Similarity:** Both names begin with an orthographically similar letter (C vs. G) in the prefix and contain the identical letter string in the infix/suffix (cept). Dosage Form: Both are capsules. Route of Administration: Both are given orally. Frequency: Both could be prescribed as once daily. Dose: Both could be prescribed as one dose.	**Orthographic Difference:** Graceptor contains the letters 'ra' in the prefix while Concept contains the letters 'on' giving the prefix of both names a different appearance when scripted. **Differentiating Product Characteristics:** Strength: No strength overlap. Graceptor XL is available in multiple strengths; therefore, a strength would need to be specified when prescribed on an order.

No.	**Proposed name:** Graceptor XL **Dosage Form:** Extended-Release Capsule **Strengths:** 0.5 mg, 1 mg, 5 mg **Usual Dose:** (b) (4)	**Failure Mode: Incorrect Product Ordered/ Selected/Dispensed or Administered because of Name confusion** **Causes (could be multiple)**	**Prevention of Failure Mode** **In the conditions outlined below, the following combination of factors, are expected to minimize the risk of confusion between these two names**
3.	Conceptrol (Nonoxynol-9) Vaginal Contraceptive Gel **Strength:** 100 mg **Usual Dose:** Insert one applicatorful vaginally not more than an hour before intercourse	**Orthographic Similarity:** Both names begin with an orthographically similar letter (C vs. G) and contain an identical letter string in the infix (cept). Dose: Both could be prescribed as one dose.	**Orthographic Difference:** Graceptor contains the letters 'or' in the suffix while Conceptrol contains the letters 'rol' which includes an upstroke 'l' at the end of the name giving the names a different shape and appearance when scripted. **Differentiating Product Characteristics:** Strength: No strength overlap. Graceptor XL is available in multiple strengths; therefore, a strength would need to be specified when prescribed on an order.
4.	Gencept 10/11 (Ethinyl Estradiol, Norethindrone) Tablet **Strength:** 0.035 mg/0.035 mg and 0.5 mg/1 mg **Usual Dose:** One tablet by mouth once daily	**Orthographic Similarity:** Both names begin with the letter 'G' and contain the identical letter string 'cept.' Route of Administration: Both are given orally. Frequency: Both could be prescribed as once daily. Dose: Both could be prescribed as one dose.	**Orthographic Difference:** Graceptor contains the additional letters 'or' in the suffix which is not seen in Gencept giving Graceptor a longer appearance when scripted. In addition, when included, the modifier 10/11 in Gencept would help differentiate their names. **Differentiating Product Characteristics:** Strength: No strength overlap. Graceptor XL is available in multiple strengths; therefore, a strength would need to be specified when prescribed on an order.

No.	Proposed name: Graceptor XL Dosage Form: Extended-Release Capsule Strengths: 0.5 mg, 1 mg, 5 mg Usual Dose: (b) (4)	Failure Mode: Incorrect Product Ordered/ Selected/Dispensed or Administered because of Name confusion Causes (could be multiple)	Prevention of Failure Mode In the conditions outlined below, the following combination of factors, are expected to minimize the risk of confusion between these two names
5.	Genoptic (Gentamicin Sulfate) Ophthalmic Solution **Strength:** 0.3% **Usual Dose:** Instill 1 or 2 drops into the affected eye every 4 hours or 2 drops once every hour (for severe infections) Genoptic SOP (Gentamicin Sulfate) Ophthalmic Ointment **Strength:** 0.3% **Usual Dose:** Apply a small amount (1/2 inch) to the affected eye 2 to 3 times daily	**Orthographic Similarity:** Both names begin with the same letter 'G' and contain a similar letter string in the infix of the name (opt vs. ept).	**Orthographic Difference:** Graceptor contains the letters 'rac' in the prefix which when scripted appears different than the letters 'en' in the prefix of Genoptic. **Differentiating Product Characteristics:** Strength: No strength overlap. Graceptor XL is available in multiple strengths; therefore, a strength would need to be specified when prescribed on an order. Dosage Form: Genoptic is available as an ophthalmic solution and ointment; therefore, a dosage form would need to be specified when prescribed on an order.

No.	**Proposed name:** Graceptor XL **Dosage Form:** Extended-Release Capsule **Strengths:** 0.5 mg, 1 mg, 5 mg **Usual Dose:** (b) (4)	**Failure Mode: Incorrect Product Ordered/ Selected/Dispensed or Administered because of Name confusion** **Causes (could be multiple)**	**Prevention of Failure Mode** **In the conditions outlined below, the following combination of factors, are expected to minimize the risk of confusion between these two names**
6.	Grisactin (Griseofulvin Microsize) **Tablet:** 500 mg **Capsule:** 125 mg, 250 mg **Usual Dose:** 125 mg to 1000 mg by mouth daily (single or divided doses)	**Orthographic Similarity:** Both names contain 9 letters, begin with the same letter string 'Gr', and contain a cross-stroke 't' in the 7th position of their names. Dosage Form: Both are available as capsules. Route of Administration: Both are given orally. Frequency: Both could be prescribed as once daily. Dose: Both could be prescribed as one dose.	**Orthographic Difference:** Graceptor contains a downstroke 'p' in the infix of the name which is not seen in Grisactin. Also, Graceptor contains the letters 'acep' in the infix and 'or' in the suffix which when scripted appear different from the letters 'isac' in the infix and 'in' in the suffix of the name Grisactin. **Differentiating Product Characteristics:** Strength: No strength overlap. Grisactin and Graceptor XL are available in multiple strengths; therefore, a strength would need to be specified when prescribed on an order.

No.	**Proposed name:** Graceptor XL **Dosage Form:** Extended-Release Capsule **Strengths:** 0.5 mg, 1 mg, 5 mg **Usual Dose:** (b) (4)	**Failure Mode: Incorrect Product Ordered/ Selected/Dispensed or Administered because of Name confusion** **Causes (could be multiple)**	**Prevention of Failure Mode** **In the conditions outlined below, the following combination of factors, are expected to minimize the risk of confusion between these two names**
7.	Herceptin (Trastuzumab) Solution **Strength:** 400 mg/20 mL **Usual Dose:** Dosing based on different indications Initial Dose: 4 mg/kg by intravenous infusion over 90 minutes, then 2 mg/kg as an intravenous infusion over 30 minutes weekly during chemotherapy for the first 12 weeks or 18 weeks or 8 mg/kg by intravenous infusion over 90 minutes. For example, an adult patient weighing 75 kg would receive a dose of 150 mg to 600 mg by	**Orthographic Similarity:** Both names contain 9 letters, and contain an identical letter string 'cept' in the infix of their names.	**Orthographic Difference:** Graceptor contains the letters 'ra' in the prefix and the letters 'or' in the suffix which when scripted appear different than the letters 'er' in the prefix and the letters 'in' in the suffix of the name Herceptin. **Differentiating Product Characteristics:** Strength: No strength overlap. Graceptor XL is available in multiple strengths; therefore, a strength would need to be specified when prescribed on an order. Frequency: by intravenous infusion over 30 to 90 minutes once weekly to every 3 weeks vs. once daily

No.	Proposed name: Graceptor XL Dosage Form: Extended-Release Capsule Strengths: 0.5 mg, 1 mg, 5 mg Usual Dose: (b) (4)	Failure Mode: Incorrect Product Ordered/ Selected/Dispensed or Administered because of Name confusion Causes (could be multiple)	Prevention of Failure Mode In the conditions outlined below, the following combination of factors, are expected to minimize the risk of confusion between these two names
	intravenous infusion. Maintenance Dose: 6 mg/kg by intravenous infusion over 30 to 90 minutes every 3 weeks or 2 mg/kg by intravenous infusion over 30 minutes, given once weekly. For example, an adult patient weighing 75 kg would receive a dose of 450 mg by intravenous infusion.		

No.	**Proposed name:** Graceptor XL **Dosage Form:** Extended-Release Capsule **Strengths:** 0.5 mg, 1 mg, 5 mg **Usual Dose:** (b) (4)	**Failure Mode: Incorrect Product Ordered/ Selected/Dispensed or Administered because of Name confusion** **Causes (could be multiple)**	**Prevention of Failure Mode** **In the conditions outlined below, the following combination of factors, are expected to minimize the risk of confusion between these two names**
8.	Effexor (Venlafaxine HCl) Tablet **Strengths:** 25 mg, 37.5 mg, 50 mg, 75 mg, 100 mg **Usual Dose:** 75 mg to 375 mg by mouth daily in 2 or 3 divided doses	**Phonetic Similarities:** Both names contain 3 syllables in which the 2nd and 3rd syllable sound similar ('ffe'-'xor' vs. 'cep'-'tor'). Route of Administration: Both are given orally. Dose: Both could be prescribed as one dose.	**Phonetic Differences:** The first syllable in both names sound distinctly different when spoken ('E' vs. 'Gra'). **Differentiating Product Characteristics:** Strength: No strength overlap. Graceptor XL and Effexor are available in multiple strengths; therefore, a strength would need to be specified when prescribed on an order. Frequency: 2 to 3 times daily vs. once daily

No.	**Proposed name:** Graceptor XL **Dosage Form:** Extended-Release Capsule **Strengths:** 0.5 mg, 1 mg, 5 mg **Usual Dose:** (b) (4)	**Failure Mode: Incorrect Product Ordered/ Selected/Dispensed or Administered because of Name confusion** **Causes (could be multiple)**	**Prevention of Failure Mode** **In the conditions outlined below, the following combination of factors, are expected to minimize the risk of confusion between these two names**
9.	Crestor (Rosuvastatin Calcium) Tablet **Strengths:** 5 mg, 10 mg, 20 mg, 40 mg **Usual Dose:** 5 mg to 40 mg by mouth once daily	**Orthographic and Phonetic Similarities:** Both names begin with an orthographically similar letter string (Cre vs. Gra) and end with the same letter string (tor). When spoken the 2nd and 3rd syllables of Graceptor sound similar to the 1st and 2nd syllables of Crestor ('cep'-'tor' vs. 'Cres'-'tor'). Route of Administration: Both are given orally. Frequency: Both could be prescribed as once daily. Dose and Strength: Dose (5 mg, 10 mg, 20 mg) and strength overlap (5 mg).	**Orthographic and Phonetic Differences:** Graceptor contains a downstroke 'p' in the infix of the name which is not seen in Crestor giving the names a different shape and appearance. When included, the modifier 'XL' in Graceptor may help differentiate both names. Graceptor contains 3 syllables while Crestor contains only 2 syllables. When spoken, the combination of the first syllable with the 2nd and 3rd syllables in the name Graceptor gives the name a distinctly different sound from the 2 syllable name Crestor.

No.	**Proposed name:** Graceptor XL **Dosage Form:** Extended-Release Capsule **Strengths:** 0.5 mg, 1 mg, 5 mg **Usual Dose:** (b) (4)	**Failure Mode: Incorrect Product Ordered/ Selected/Dispensed or Administered because of Name confusion** **Causes (could be multiple)**	**Prevention of Failure Mode** **In the conditions outlined below, the following combination of factors, are expected to minimize the risk of confusion between these two names**
10.	Genaspor (Tolnaftate) Cream **Strength:** 1% **Usual Dose:** Apply topically twice daily	**Orthographic and Phonetic Similarities:** Both names begin with the same letter 'G', contain a downstroke 'p' in the 6th position, and the identical letter string 'or' in the suffix of their names. When spoken, both names contain 3 syllables in which the last syllable sounds similar ('por' vs. 'tor').	**Orthographic and Phonetic Differences:** Graceptor contains a cross-stroke 't' in the suffix of the name which is not seen in Genaspor giving both names a different shape and appearance. Also, Graceptor contains the letters 'race' in the prefix while Genaspor contains the letters 'enas' in the prefix which appears different when scripted. When spoken, the first 2 syllables in both names sound distinctly different ('Gen'-'as' vs. 'Gra'-'cep'). **Differentiating Product Characteristics:** Strength: No strength overlap. Graceptor XL is available in multiple strengths; therefore, a strength would need to be specified when prescribed on an order.

No.	**Proposed name:** Graceptor XL **Dosage Form:** Extended-Release Capsule **Strengths:** 0.5 mg, 1 mg, 5 mg **Usual Dose:** (b) (4)	**Failure Mode: Incorrect Product Ordered/ Selected/Dispensed or Administered because of Name confusion** **Causes (could be multiple)**	**Prevention of Failure Mode** **In the conditions outlined below, the following combination of factors, are expected to minimize the risk of confusion between these two names**
11.	Rescriptor (Delavirdine Mesylate) Tablet **Strengths:** 100 mg, 200 mg **Usual Dose:** 400 mg by mouth 3 times daily	**Orthographic and Phonetic Similarities:** Both names contain a similar letter string (iptor vs. eptor) in the suffix of their names. When spoken, both names contain 3 syllables in which the 2nd and 3rd syllables sound similar ('scrip'-'tor' vs. 'cep'-'tor'). Route of Administration: Both are given orally. Dose: Both could be prescribed as one dose.	**Orthographic and Phonetic Differences:** Graceptor begins with an orthographically different letter string than Rescriptor (Grac vs. Rescr) which when scripted, appears different. When spoken, the first syllable in both names sound distinctly different ('Re' vs. 'Gra'). **Differentiating Product Characteristics:** Strength: No strength overlap. Rescriptor and Graceptor XL are available in multiple strengths; therefore, a strength would need to be specified when prescribed on an order. Frequency: 3 times daily vs. once daily

Appendix F: Risk Mitigation Strategies Implemented in the EU by Astellas

(1) Revised the Advagraf product information in their package insert (December 2008) to include a statement that Advagraf is a once-a-day oral formulation of tacrolimus and that inadvertent, unintentional or unsupervised switching of immediate-release or prolonged-release formulations of tacrolimus is unsafe

(2) Added warnings regarding reports of medication errors between the immediate-release and extended-release formulations to the package insert

(3) Revised the over-labeling of Advagraf's outer packaging highlighting the once-daily regimen which received approval by the European Commission (EC) on March 25, 2009.

(4) The safety concerns of inadvertent switching between the immediate-release and extended-release formulations were communicated in a Dear Healthcare Professional (DHCP) letter in December 2008.

(5) Modifications to the product information in the package insert for Prograf were approved in the majority of EU countries in April 2009.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JUNG E LEE
04/04/2013

JAMIE C WILKINS PARKER
04/04/2013

KELLIE A TAYLOR
04/04/2013

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Proprietary Name Review

Date:	November 19, 2012
Reviewer:	Jung Lee, RPh Division of Medication Error Prevention and Analysis
Team Leader:	Jamie Wilkins Parker, PharmD Division of Medication Error Prevention and Analysis
Deputy Director:	Kellie Taylor, PharmD, MPH Division of Medication Error Prevention and Analysis
Director:	Carol Holquist, RPh Division of Medication Error Prevention and Analysis
Drug Name and Strengths:	Advagraf (Tacrolimus Extended-release) Capsules, 0.5 mg, 1 mg, 5 mg
Application Type/Number:	IND 064148 and NDA 204096
Sponsor:	Astellas Pharma, Inc
OSE RCM #:	2012-1212 and 2012-2549

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

CONTENTS

1 INTRODUCTION

This review evaluates the proposed proprietary name, Advagraf, from a safety and promotional perspective. The sources and methods used to evaluate the proposed name are outlined in the reference section and Appendix A respectively.

1.1 REGULATORY HISTORY

The Applicant initially submitted three NDAs for this product: NDA 050811 (prevention of rejection in renal transplantation), NDA 050815 (prevention of rejection in liver transplantation), and NDA 050816 (prevention of rejection in heart transplantation). The Division took an approvable action for NDAs 050815 and 050811 on January 19, 2007. NDA 050816 received a Not Approvable on the same date. (b) (4)

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During the aforementioned review cycles, the Applicant submitted three proprietary names for evaluation. The first proposed name, Prograf MR (OSE #06-0114, dated 4/20/2006) was not recommended by DMEPA, formerly known as DMETS (the Division of Medication Error and Technical Support), due to the use of the modifier "MR" in conjunction with the proprietary name since modified-release capsule is not a USP recognized dosage form. The second proposed name, Prograf XL (OSE #2006-143, dated 9/7/2006) was found acceptable by DMETS because the name followed traditional nomenclature practices for extended-release formulations. However, following this review DMETS learned that the products were not the same and therefore indicated to the review division that confusion may occur between Prograf and Prograf XL due to their overlapping strengths and practitioners unfamiliarity with the new product and the fact that these products were different. Thus, the Division informed the Applicant that Prograf XL was unacceptable via responses to questions posted in the Applicant's briefing package dated March 20, 2007. The Division requested the Applicant use the name Advagraf in order to harmonize the name internationally, since it is marketed in Europe as Advagraf (approved in Europe in April 2007 and launched in October 2007), and to minimize potential confusion between Prograf and Prograf XL. Therefore, the Division submitted a consult requesting DMETS review the proprietary name, Advagraf, on March 22, 2007. On January 23, 2008, DMETS found the name acceptable from a safety perspective in OSE #2007-2052. However, the Division of Prescription Drug Promotion (OPDP)'s, formerly Drug Marketing Advertising and Communications (DDMAC), objected to the proprietary name from a promotional perspective on April 5, 2007 and October 4, 2007. DDMAC was previously overruled in the first two objections by the Division of Transplant and Ophthalmology (formerly known as the Division of Special Pathogen and Transplant Products) in 2007 due to their desire to harmonize the name internationally and because of safety concerns identified with the product.

On May 22, 2012, the Sponsor resubmitted the proposed proprietary name, Advagraf under IND 064148 with an indication for use in patients receiving kidney transplants and male patients receiving liver transplants only. On October 25, 2012, the Request for Proprietary Name Review was also submitted by the Applicant under NDA 204096. This review summarizes the outcome of these most recent requests for evaluation of Advagraf.

1.2 PRODUCT INFORMATION

The following product information is provided in the May 22, 2012 proprietary name submission.

- Active Ingredient: Tacrolimus
- Indication of Use:
  - Prophylaxis of organ rejection in adult patients receiving kidney transplants
  - Prophylaxis of organ rejection in male patients receiving liver transplants
- Route of Administration: Oral
- Dosage Form: Extended-Release Capsules
- Strength: 0.5 mg, 1 mg, 5 mg
- Dose and Frequency: Once daily oral administration. The dosage of Advagraf is tailored to each patient. (b) (4)
- How Supplied: 30-count bottles and 5 blister sheets of 10 capsules
- Storage: Store at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) (USP Controlled Room Temperature)

2 RESULTS

The following sections provide the information obtained and considered in the overall evaluation of the proposed proprietary name.

2.1.1 United States Adopted Names (USAN) Search

The September 28, 2012 search of the United States Adopted Name (USAN) stems did not identify that a USAN stem is present in the proposed proprietary name.

2.1.2 Components of the Proposed Proprietary Name

The Applicant indicated in their submission that the proposed name, Advagraf, was not derived from any particular concept and does not have any intended meaning. This proprietary name is comprised of a single word that contains the prefix "Adva" and the suffix "graf".

2.1.3 FDA Name Simulation Studies

Twenty-eight practitioners participated in DMEPA's prescription studies. The interpretations did not overlap with or appear/sound similar to any currently marketed products. Ten out of 28 prescription study participants correctly interpreted the name Advagraf. Of the participants who correctly interpreted the name, seven were from the outpatient study, three from the inpatient study, and none from the verbal study. Of the inpatient participants who misinterpreted the name, all of them misinterpreted the letter 'v' in Advagraf with either the letters 'e', 'r', or 'l'. A common misinterpretation in the

outpatient study was the incorrect interpretation of the letter 'a' in the 7th position of the name Advagraf with the letter 'o' and the prefix 'Ad' with 'At' or 'Slu'. See Appendix C for the complete listing of interpretations from the verbal and written prescription studies.

2.1.4 Failure Mode and Effects Analysis of Similar Names to Advagraf

Appendix B lists possible orthographic and phonetic misinterpretations of the letters appearing in the proposed proprietary name, Advagraf. Table 1 lists the names with orthographic, phonetic, or spelling similarity to the proposed proprietary name, Advagraf identified by the primary reviewer, the Expert Panel Discussion (EPD), and other review disciplines. Table 1 also includes the names identified by Addison Whitney Health, not identified by DMEPA, which require further evaluation.

Table 1: Collective List of Potentially Similar Names (DMEPA, EPD, Other Disciplines, and Addison Whitney Health External Name Study)

Look Similar		**Look Similar**		**Look Similar**	
Name	***Source***	***Name***	***Source***	***Name***	***Source***
Accupril	AW	Advate	FDA	Atripla	FDA
Adagen	FDA	Advicor	FDA	Atropine	FDA
Adipex	FDA	Alprazolam	AW	Avandaryl	AW
Adipoxil	FDA	Anastrozole	AW	Ciclopirox	FDA/Primary SE
Adroyd	FDA	Androderm	AW	Colazal	FDA
Adrucil	FDA	Androgel	AW	Gengraf	FDA
Advacal	FDA	Atapro	FDA		
Look and Sound Similar		**Look and Sound Similar**		**Look and Sound Similar**	
Advair	FDA	Avandia	AW	Prograf	FDA/AW
Advil	AW	Avodart	FDA/AW	Viagra	AW

Our analysis of the 26 names contained in Table 1 considered the information obtained in the previous sections along with their product characteristics. We determined 26 names will not pose a risk for confusion as described in Appendices D through E.

2.1.5 Promotional Assessment at Initial Phase of Proprietary Name Review

On May 31, 2012, the Office of Prescription Drug Promotion (OPDP) found the name Advagraf unacceptable because it overstates the efficacy of the drug product and implies superiority. OPDP stated the prefix "Adva" in the proposed proprietary name evokes the word "advantage," which is defined as "the quality or state of being superior: a more favorable or improved position or condition" (http://unabridged.merriam-webster.com/cgi-bin/unabridged accessed 5/31/12). Therefore, the proposed proprietary name misleadingly suggests that this extended-release tacrolimus product has an

"advantage" and is somehow superior to other drugs approved for the same indication(s), including other tacrolimus products, such as Prograf. Without substantial evidence to support that this extended-release tacrolimus product is safer or more effective than other drugs approved for the same indication(s), including other tacrolimus products, the proposed proprietary name is misleading."

In response to OPDP's objection the Division of Transplant and Ophthalmology Products (DTOP) provided the following comment at the initial phase of the proprietary name review:

> *This was discussed before and last time Advagraf was accepted to distinguish it from Prograf (and FDA turned down the company's request to use Prograf XL or Prograf XE). While I acknowledge OPDP's observation, I would not make that the reason to object to the name in this case.*
>
> *We had initially considered that Advagraf and Prograf were different enough so the medication mixup between them could be preventable. Since then, we have data based on European marketing and DMEPA is reviewing that. Currently, DMEPA approves trade names, not OND. So my request would be that DMEPA decide whether to accept the name. The naming goal should be to help pharmacists, HCP and patients distinguish Advagraf and Prograf.*

In order for DMEPA to determine if the name Advagraf should be allowed for safety reasons despite OPDP's objection, we requested further information from the Sponsor in an information request. Additionally, DMEPA held a teleconference with the Sponsor, DTOP and OPDP on September 12, 2012. At this teleconference, the promotional concerns were communicated to the sponsor and answers to DMEPA's informational request were discussed. DMEPA's information request from the September 12, 2012 teleconference was provided to the Sponsor prior to the call and is referenced in their Response to the Office of Prescription Drug Promotion (OPDP) submission (pages 3 to 13). The Sponsor understood OPDP's objection but wanted to know why DTOP and DMEPA previously agreed to allow the use of the name Advagraf (NDA 50-815 Advagraf fax communication dated 1/23/2008). DMEPA explained the basis of the current objection and outlined a path forward for the firm to address the Agency's promotional concern and requested they provide rationale for why they want to pursue the name Advagraf for safety reasons despite OPDP's objection. The data provided in support of retention of the Advagraf name is discussed in the following sections.

2.1.6 Applicant's Data to Support the Continued Use of Advagraf for Safety Reasons

To support the continued use of the proprietary name Advagraf, the Applicant described the steps taken to mitigate errors between Prograf and Advagraf in the European Union (EU), provided a listing of all postmarketing medication errors received since 2007, provided their Periodic Safety Update Reports (PSURs), and provided a response to OPDP's objection. Additionally, the Applicant continues to believe that harmonization of the name in their major markets (EU and US) would help minimize the confusion between Advagraf and Prograf.

2.1.6.1 Evaluation of the Risk Minimization Measures Implemented in the EU

The Applicant provided a listing of all 152 international post-marketing medication error narratives since 2007. Some of the medication error cases were missing event dates and therefore it was not possible to ascertain the time period in which these medication errors occurred. Thus, we evaluated the listing of medication errors from the Periodic Safety Update Reports (PSURs) in order to evaluate the time line of events in relation to the risk mitigation strategies for Advagraf and Prograf (implemented in December 2008 and April 2009). We note the PSURs only include 125 medication errors from the EU through March 2012; however, the 152 medication error narratives also includes cases through August 2012 and 21 additional cases from non-EU countries in which tacrolimus extended-release capsules are approved. Table 1 provides a listing of medication errors from the PSURs involving Advagraf and Prograf. Figure 1 provides the number of Advagraf/Prograf medication error cases reported per six months (PSUR 13 to PSUR 20).

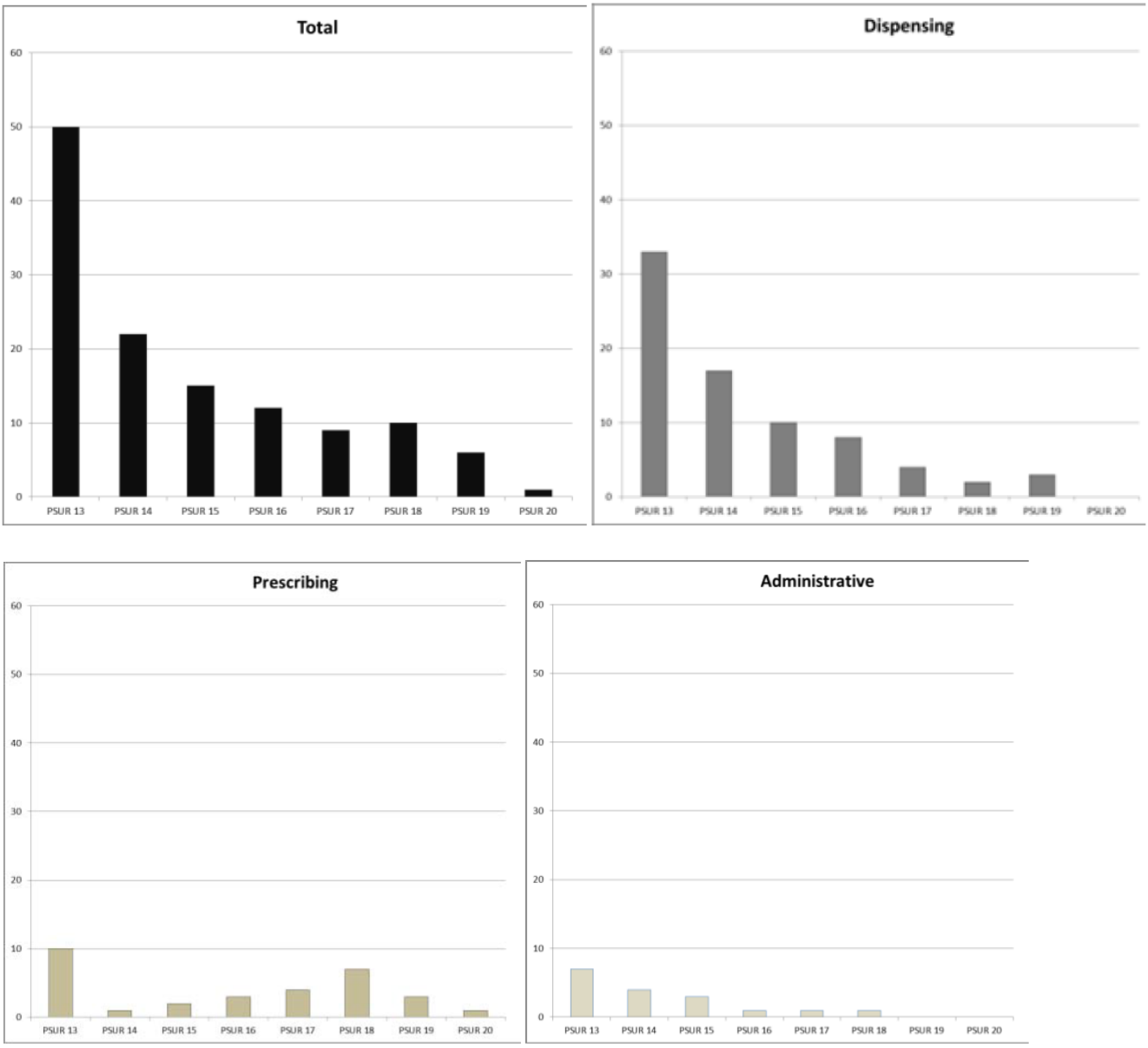
Table 1: PSUR- Listings of Medication Errors involving Advagraf and Prograf

PSUR mm/yy to mm/yy	Prescribing Errors	Dispensing Errors	Administration Errors	Total
PSUR 13 04/08 to 09/08	10	33	7	50
PSUR 14 10/08 to 03/09	1	17	4	22
PSUR 15 04/09 to 09/09	2	10	3	15
PSUR 16 10/09 to 03/10	3	8	1	12
PSUR 17 04/10 to 09/10	4	4	1	9
PSUR 18 10/10 to 03/11	7	2	1	10
PSUR 19 04/11 to 09/11	3	3	0	6
PSUR 20 10/11 to 03/12	1	0	0	1
Total	**31**	**77**	**17**	**125**

PSUR: Periodic Safety Update Report.

Note: Medication errors are drug prescribing errors, drug dispensing errors and drug administration errors where Prograf was prescribed, dispensed or administered in place of Advagraf, or vice versa.

Figure 1: Number of Advagraf/Prograf Medication Error cases reported per six months (PSUR 13 to PSUR 20)



Clockwise: The total number of A/P ME errors; A/P ME errors due to dispensing errors; A/P ME errors due to prescribing errors; A/P ME errors due to administration errors.

PSUR 13: April 2008 - September 2008; PSUR 14: October 2008 - March 2009

PSUR 15: April 2009 - September 2009 ; PSUR 16: October 2009 - March 2010

PSUR 17: April 2010 - September 2010; PSUR 18: October 2010 - March 2011

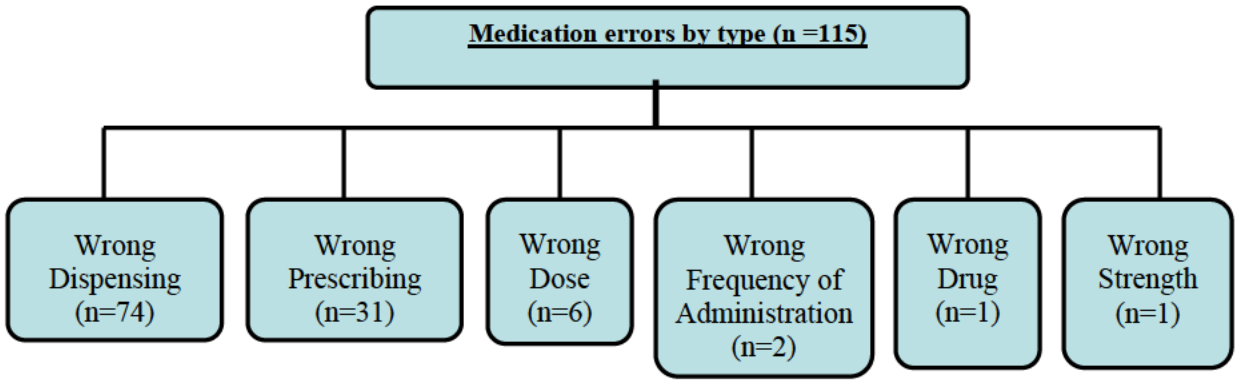
PSUR 19: April 2011 - September 2011; PSUR 20: October 2011 - March 2012

After individual review of the 152 medication error cases submitted by the Applicant, 37 cases were excluded for the following reasons:

- Cases not related to confusion between tacrolimus immediate-release and extended-release formulations
  - Drug interactions
  - Product quality issues
  - Extra dose taken mistakenly by the patient
  - Noncompliance
  - Overdose unrelated to confusion between tacrolimus immediate-release and extended-release formulations
  - Wrong route of administration error
  - Wrong technique of administration error

Figure 2 below provides a stratification of the remaining 115 cases by type of error.

Figure 2: Tacrolimus immediate-release and extended-release medication errors categorized by type of error (n = 115)



The majority of the 115 medication error cases involving confusion between Advagraf and Prograf were from the United Kingdom (n=70 cases), of which 50 involved dispensing errors, 19 cases were prescribing errors, and 1 case reported dispensing the wrong dose of the extended-release and immediate-release tacrolimus capsules. Based on our assessment of these cases, none of these medication errors appear to be linked to confusion between the proprietary names used for tacrolimus extended-release (Advagraf, Prograf XL, and Graceptor) and tacrolimus immediate-release (Prograf) capsules. The Applicant stated the potential root causes for the medication errors were a lack of education and awareness, poor communication between healthcare professionals and patient, prescribing by INN, ambiguity of the prescribing, ordering and dispensing

computer system, price differences and possibly due to similarities in the outer-packaging of Advagraf and Prograf. In the United Kingdom, prescribing is done with the use of International Nonproprietary Names (INN) (tacrolimus) instead of by proprietary names.[1] According to the Applicant, the identical INN, in addition to not specifying the immediate-release or extended-release formulation, accounts for the majority of erroneous prescribing and/or dispensing of the unintended formulation in the UK.

To mitigate errors between Prograf and Advagraf the Applicant implemented the following risk minimization measures in the EU (1) revised the Advagraf product information in their package insert (December 2008) to include a statement that Advagraf is a once-a-day oral formulation of tacrolimus and that inadvertent, unintentional or unsupervised switching of immediate-release or prolonged-release formulations of tacrolimus is unsafe; (2) added warnings regarding reports of medication errors between the immediate-release and extended-release formulations to the package insert; and (3) revised the over-labeling of Advagraf's outer packaging highlighting the once-daily regimen which received approval by the European Commission (EC) on March 25, 2009. The safety concerns of inadvertent switching between the immediate-release and extended-release formulations were also communicated in a Dear Healthcare Professional (DHCP) letter in December 2008. Modifications to the product information in the package insert for Prograf were also approved in the majority of EU countries in April 2009.

The Applicant states that since implementing the aforementioned risk minimization measures, there has been a marked decrease in the overall number of medication errors, particularly in the number of dispensing and administration errors; however, prescribing errors appear to have remained stable. To evaluate these claims, we reviewed the table listing 125 medication errors from the Applicant's Periodic Safety Update Reports (PSURS) dated April 2008 to March 2012, to determine if there was data to support the assertion that marketing the product with the Advagraf name helped to decrease dispensing, administration, and prescribing errors associated with tacrolimus extended-release and immediate-release capsules. The table included the total number of medication error cases involving Advagraf and Prograf as a result of prescribing, dispensing, and administration errors. We compared the PSURs from April 2008 to September 2009 (PSUR 13 to PSUR 15) with the PSURs from October 2009 to March 2012 (PSUR 16 to PSUR 20) to compare the number of medication errors reported before and after the risk minimization strategies were implemented (DHCP implemented in December 2008 and changes to the label and labeling in April 2009).

The review of the PSURS from April 2008 to September 2009 show there were 87 error cases (13 prescribing errors, 60 dispensing errors, and 14 administration errors). The PSURS from October 2009 to March 2012 (PSUR 16 to PSUR 20) include a total of 38 error cases (18 prescribing errors, 17 dispensing errors, and 3 administration errors)

[1] Generics and Biosimilars Initiative (GaBI) . Policies and Legislation Posted 12/08/2011. http://www.gabionline.net/layout/set/print/Country-Focus/United-Kingdom/Policies-and-Legislation

representing a slight decline in the total number of reported medication errors since issuing the DHCP letter, making modifications to Advagraf and Prograf's package insert, as well as over-labeling Advagraf's outer packaging emphasizing the once-daily dosing regimen. However, our assessment found a greater number of prescribing errors involving Advagraf and Prograf reported post-implementation of the safety measures.

After implementation of the safety measures from December 2008 through April 2009, the number of dispensing errors reported from October 2009 to March 2012 (17 vs. 60 prior to October 2009) is less, as are the number of administration errors (3 vs. 14 prior to October 2009). However, due to the limitations of spontaneous reporting, it is impossible to know if the differences in the absolute number of medication error cases reflect an actual change in the number of error occurrences. It is possible that the difference in the number of cases is a reflection of changes in reporting habits over the period of time (i.e. reporting fatigue or even stimulated reporting due to HCP outreach). Furthermore, after reviewing the case narratives we are not able to determine which of the safety measures were effective at reducing errors (if any).

The risk minimization strategies focused on resolving the knowledge deficit among practitioners concerning the difference between the extended-release and immediate-release tacrolimus products, highlighting the differences in dosing regimens, and including a warning that medication errors have occurred involving inadvertent, unintentional or unsupervised substitution of immediate-release or extended-release tacrolimus formulations.

Based on our review of the medication errors, we found that none of the confusion between the extended-release and immediate-release products was attributed to proprietary name confusion. The confusion between the immediate-release tacrolimus and extended-release tacrolimus products appear to be a result of similarities in product characteristics. Both these products contain the same active ingredient (tacrolimus), they share an overlapping dosage form (capsules), route of administration (oral), and strengths (0.5 mg, 1 mg, 5 mg) as well as similar indications for use, prescribers, and similar patient population. Therefore, based on the description of the risk minimization measures and our evaluation of the medication error cases reported in the EU and other countries, we are unable to conclude that Advagraf offers any particular safety advantage over another proprietary name since we could not link any of the risk minimization measures or the effectiveness of these measures to the use of the name Advagraf.

Additionally, since confusion between the immediate-release and extended-release tacrolimus products have been associated with confusion regarding the actual dosing regimen (once daily vs. twice daily) and more specifically to confusion between the difference in the immediate-release and extended-release formulations, we evaluated the need for a modifier in the proprietary name. Including a modifier, such as 'XL', with a new root name may help further convey the once daily dosing regimen. The new root name plus modifier may help practitioners identify that there is something different about this product and may help to prevent wrong drug errors. If a new root name plus a modifier were used for this product and the modifier was omitted during prescribing, the wrong drug would not be dispensed because the new root name is not commercially

available in any other formulation. Unlike the name Prograf XL, where the possibility exists for the immediate-release Prograf, to be dispensed if the modifier was mistakenly omitted, the new unique root name plus modifier would not result in the same medication error. Thus, we believe that a unique proprietary name which is not promotional and not orthographically or phonetically similar to other proprietary or established names, and that more clearly communicates to the healthcare provider that the proposed product is an extended-release, once-daily formulation may be a better naming convention.

2.1.6.2 Harmonization of the Name Advagraf

The Applicant stated that FDA requested they use the name Advagraf as the brand name for tacrolimus extended-release capsules in March 2007. At that time, Advagraf was the only proprietary name approved anywhere in the world for this product. The rationale provided by FDA was that the use of the name Advagraf would harmonize the name internationally and would reduce confusion and accidental interchange of the medications (Prograf and Advagraf). The Applicant continues to believe that harmonization of the name in their 2 major markets (EU and US) would help minimize the confusion between Advagraf and Prograf. The Applicant states the name Advagraf is already well established in the global transplant community. To illustrate the global nature of transplantation, the Applicant cited 13 out of 34 tacrolimus once-daily abstracts presented at the American Transplant Congress (ATC), the premier meeting of transplant specialists worldwide, referenced the once-daily tacrolimus as Advagraf. They state that once-daily tacrolimus is already referred to as Advagraf in the US; therefore, adoption of this name has the potential to reduce the risk of additional medication errors. However, DMEPA notes the remaining 21 (or the majority of abstracts) did not refer to the tacrolimus extended-release as Advagraf. In any case, it is unclear how the use of the name Advagraf in some of the published literature will help to reduce the risk of additional medication errors.

Since receiving approval of the name Advagraf in Europe in 2007 (currently approved in 50 countries as Advagraf), tacrolimus extended-release capsules have also been approved in many other countries under several different names (Prograf XL in 17 Latin American countries and in Australia and New Zealand, Graceptor in Japan , and Tacrolimus Sustained-Release in China) (See Appendix F). Therefore, the harmonization rationale would not apply in this case since there are several proprietary names approved and in use internationally for tacrolimus extended-release capsules.

2.1.6.3 Response to OPDP Objection

OPDP stated the proposed proprietary name misleadingly suggests that this extended-release tacrolimus product has an "advantage" and is somehow superior to other drugs approved for the same indication(s), including other tacrolimus products, such as Prograf.

In response to OPDP's promotional concern, the Applicant states in their written Response to the Office of Prescription Drug Promotion submission received October 3, 2012 that "although Advagraf and "advantage" both start with the same four letters, the pronunciation of each is clearly differentiated (AD-va-graf versus ad-VAN-tage), with the accent on the first syllable for Advagraf and on the second syllable for advantage. The Applicant states that none of the claims for Advagraf are superiority claims; the only

claims are non-inferiority claims to current therapies. Astellas notes that there are other marketed drugs that begin with the 3-letter triad "ADV": Advair, Advicor, and Advil."

OPDP provided a response in a Proprietary Name Rebuttal Response memorandum dated November 2, 2012 stating that in the absence of behavioral data that shows that people will not associate "Advagraf" with "advantage", they are not persuaded. OPDP further stated that despite the Applicant's claims that there are other FDA-approved drugs that begin with the letters "Adv", OPDP's concern stems from the four-letter prefix "Adva", which in their opinion, evokes "advantage", not the three-letter prefix "Adv".

In response to the Applicant's claims that none of the claims for Advagraf are superiority claims and that the only claims are non-inferiority claims to current therapies, OPDP responded that given the definition of "advantage" and the lack of behavioral data to suggest consumers will not associate "Advagraf" with "advantage", they are not persuaded to change their opinion about the misleading nature of the name.

OPDP acknowledges that the name "Advagraf" was chosen to harmonize the name internationally and reduce confusion and accidental interchange of immediate-release and extended-release tacrolimus. OPDP further acknowledges that safety is an important consideration in the proprietary name evaluation process; however, OPDP stated they primarily review proposed proprietary names from a promotional perspective.

DMEPA reviewed ODPD's promotional assessment and the information provided by the Applicant in support of the Advagraf name. Like OPDP, we find the Applicant has not provided convincing data to demonstrate that the public will not associate Advagraf with "advantage". Given the absence of convincing data provided by the Applicant to address the promotional concerns outlined by OPDP, DMEPA concurs with OPDP's finding that the name Advagraf is misleading.

3 INTEGRATED ASSESSMENT OF THE NAME ADVAGRAF

The confusion between the immediate-release and extended-release products lies with the inadvertent substitution of the different formulations due to confusion with the established names, dosing regimen, and overlapping product characteristics. Thus, differentiating the two products through distinct proprietary names and emphasizing the difference in formulations and dosing regimen is likely to help reduce medication errors and ensure the safe use of this product. Although Advagraf is unique from Prograf, the proposed name Advagraf was found to be promotional and does not appear to offer any discernable safety advantage for this product over any other unique proprietary name that could be used to market extended-release tacrolimus in the United States. Additionally, the Applicant's interest in harmonizing the name globally is not achievable given the approval of the extended-release tacrolimus under different proprietary names (Graceptor, Prograf XL) in non-EU countries.

A new proprietary name which is not promotional and not orthographically or phonetically similar to other proprietary or established names is a more viable naming approach from a regulatory perspective. Furthermore, since most medication errors for Advagraf and Prograf seem to involve confusion of the established names, knowledge deficit that Advagraf is an extended-release formulation, or confusion about the dosing frequency (once daily), we conclude that the inclusion of a modifier, such as 'XL', in the

unique proprietary name may help convey that this product is an extended-release formulation and further minimize confusion of these products. In addition, despite the rationale provided in support of global harmonization, our analysis concludes that it would be possible for transplant specialists as well as other healthcare professionals to learn to associate tacrolimus extended-release capsules with a new name if a new name for the extended-release tacrolimus product was introduced. From the types of medication errors reported, it is not reasonable to assume a new name would necessarily lead to more confusion than what is already reported with Advagraf and Prograf nor is there data to indicate that the introduction of the proposed name Advagraf would help to reduce the errors reported with extended-release tacrolimus products.

DMEPA communicated our decision to the Division of Transplant and Ophthalmology Products during the filing meeting on November 5, 2012. At that time we also requested additional information or concerns that could inform our review. During the filing meeting, the Division of Transplant and Ophthalmology Products stated no additional concerns with our decision or the proposed proprietary name, Advagraf.

4 CONCLUSIONS

The proposed proprietary name is unacceptable from a promotional perspective. This decision will be communicated to the Applicant with the comments in section 4.1 via letter.

Additionally, given the naming options available for tacrolimus extended-release capsules, the proposed product can be marketed under a new unique proprietary name with a modifier. We believe this is a safer naming option for this product. Thus, this information will also be communicated to the Applicant via letter (See section 4.1).

If you have further questions or need clarifications, please contact Karen Townsend, OSE project manager, at 301-796-5413.

4.1 COMMENTS TO THE APPLICANT

We have completed our review of the proposed proprietary name, Advagraf, and have concluded that the name is unacceptable for the following reasons:

1. The data provided in support of the proposed proprietary name did not persuade the Agency to change their opinion about the misleading nature of the proprietary name. You state that "although Advagraf and "advantage" both start with the same four letters, the pronunciation of each is clearly differentiated (AD-va-graf versus ad-VAN-tage) with the accent on the first syllable for Advagraf and on the second syllable for advantage. However, you did not provide data that demonstrates people will not associate "Advagraf" with "advantage".

   Additionally, you provided examples of other marketed drugs that begin with the 3-letter triad "Adv": Advair, Advicor, and Advil". However, the concern stems from the four-letter prefix "Adva", which in the Agency's opinion, evokes "advantage", not the three-letter prefix "Adv". DMEPA notes the name Advair contains the four-letter prefix "Adva", however, when the proprietary name Advair was first approved in August 2000, the Office of Prescription Drug Promotion (OPDP) did not review the name.

Therefore the Agency maintains the promotional objection to the proposed proprietary name "Advagraf" because it overstates the efficacy of the drug product and it implies superiority. The prefix "Adva" in the proposed proprietary name evokes the word "advantage," which is defined as "the quality or state of being superior: a more favorable or improved position or condition" (http://unabridged.merriam-webster.com/cgi-bin/unabridged accessed 5/31/12). Thus, the proposed proprietary name misleadingly suggests that this extended-release tacrolimus product has an "advantage" and is somehow superior to other drugs approved for the same indication(s), including other tacrolimus products, such as Prograf.

Please note that the Federal Food Drug and Cosmetic Act provides that labeling or advertising can misbrand a product if misleading representations are made, whether through a proposed proprietary name or otherwise; this includes suggestions that a drug is better, more effective, useful in a broader range of conditions or patients, safer, has fewer, or lower incidence of, or less serious side effects or contraindications than has been demonstrated by substantial evidence or substantial clinical experience [21 U.S.C. 321(n); see also 21 U.S.C. 352(a) & (n); 21 CFR 202.1(e)(5)(i);(e)(6)(i)].

2. We acknowledge that the Division of Transplant and Ophthalmology Products (DTOP) previously requested you use the name Advagraf as the proprietary name for tacrolimus extended-release capsules to harmonize the name for this product internationally and to help reduce confusion and accidental interchange of the medications (Advagraf and Prograf). At that time, Advagraf was the only proprietary name approved anywhere in the world for this product. You cited 13 out of 34 tacrolimus once-daily abstracts presented at the American Transplant Congress (ATC) reference the once-daily tacrolimus as Advagraf, to demonstrate the product is known globally as Advagraf. However, 21 (or the majority of these abstracts) make no reference to the name Advagraf. Moreover, it is unclear as to how the use of the name Advagraf in some of the published literature will help to reduce the risk of additional medication errors. Furthermore, since receiving approval of Advagraf in Europe in 2007, tacrolimus extended-release capsules have also been approved in many other countries under several different proprietary names. Therefore, global harmonization is impossible.

3. Based on the information provided, the confusion between Advagraf and Prograf is primarily due to confusion between the different formulations and dosing regimens. Because Advagraf and the currently marketed Prograf products are dosed with a different frequency of administration and inadvertent substitution could lead to significant safety issues, we recommend a modifier be appended to the proprietary name that highlights the extended release properties of the proposed product. Therefore, we recommend you submit a new unique proprietary name (not Advagraf or Prograf) with a modifier, such as ‘Proprietary name XL’, to further reduce the potential for confusion with the immediate-release tacrolimus products.

5 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. This database also lists the orphan drugs.

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

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

5. ***Division of Medication Errors Prevention and Analysis proprietary name 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. ***U.S. Patent and Trademark Office (http://www.uspto.gov)***

   USPTO provides information regarding patent and trademarks.

8. ***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.

9. ***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.

10. ***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.

11. ***Access Medicine (www.accessmedicine.com)***

    Access Medicine® from McGraw-Hill contains full-text information from approximately 60 titles; it includes tables and references. Among the titles are: Harrison's Principles of Internal Medicine, Basic & Clinical Pharmacology, and Goodman and Gilman's The Pharmacologic Basis of Therapeutics.

12. ***USAN Stems (http://www.ama-assn.org/ama/pub/about-ama/our-people/coalitions-consortiums/united-states-adopted-names-council/naming-guidelines/approved-stems.shtml)***

    USAN Stems List contains all the recognized USAN stems.

13. ***Red Book (www.thomsonhc.com/home/dispatch)***

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

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

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

15. ***Medical Abbreviations (www.medilexicon.com)***

    Medical Abbreviations dictionary contains commonly used medical abbreviations and their definitions.

16. ***CVS/Pharmacy (www.CVS.com)***

    This database contains commonly used over the counter products not usually identified in other databases.

17. ***Walgreens (www.walgreens.com)***

    This database contains commonly used over the counter products not usually identified in other databases.

18. ***Rx List (www.rxlist.com)***

    RxList is an online medical resource dedicated to offering detailed and current pharmaceutical information on brand and generic drugs.

19. ***Dogpile (www.dogpile.com)***

    Dogpile is a Metasearch engine that searches multiple search engines including Google, Yahoo! and Bing, and returns the most relevant results to the search.

20. ***Natural Standard (http://www.naturalstandard.com)***

    Natural Standard is a resource that aggregates and synthesizes data on complementary and alternative medicine.

APPENDICES

Appendix A

FDA's Proprietary Name Risk Assessment considers the promotional and safety aspects of a proposed proprietary name. The promotional review of the proposed name is conducted by OPDP. OPDP evaluates proposed proprietary names to determine if they are overly fanciful, so as to misleadingly imply unique effectiveness or composition, as well as to assess whether they contribute to overstatement of product efficacy, minimization of risk, broadening of product indications, or making of unsubstantiated superiority claims. OPDP provides their opinion to DMEPA for consideration in the overall acceptability of the proposed proprietary name.

The safety assessment is conducted by DMEPA. DMEPA staff search a standard set of databases and information sources to identify names that are similar in pronunciation, spelling, and orthographically similar when scripted to the proposed proprietary name. Additionally, we consider inclusion of USAN stems or other characteristics that when incorporated into a proprietary name may cause or contribute to medication errors (i.e., dosing interval, dosage form/route of administration, medical or product name abbreviations, names that include or suggest the composition of the drug product, etc.). 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. [2]

Following the preliminary screening of the proposed proprietary name, DMEPA gathers to discuss their professional opinions on the safety of the proposed proprietary name. This meeting is commonly referred to the Center for Drug Evaluation and Research (CDER) Expert Panel discussion. DMEPA also considers other aspects of the name that may be misleading from a safety perspective. DMEPA staff conducts a prescription simulation studies using FDA health care professionals. When provided, DMEPA considers external proprietary name studies conducted by or for the Applicant/Sponsor and incorporates the findings of these studies into the overall risk assessment.

The DMEPA primary reviewer assigned to evaluate the proposed proprietary name 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 misleading nature of the proposed proprietary name with a focus on the avoidance of medication errors.

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. DMEPA considers the product characteristics associated with the proposed product 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.

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

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. DMEPA considers how these product characteristics may or may not be present in communicating a product name throughout the medication use system. Because drug name confusion can occur at any point in the medication use process, DMEPA 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]

The DMEPA considers the spelling of the name, pronunciation of the name when spoken, and appearance of the name when scripted. DMEPA compares the proposed proprietary name with the proprietary and established name of existing and proposed drug products and names currently under review at the FDA. DMEPA 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. DMEPA examines the phonetic similarity using patterns of speech. If provided, DMEPA will consider the Sponsor's intended pronunciation of the proprietary name. However, DMEPA also considers a variety of pronunciations that could occur in the English language because the Sponsor has little control over how the name will be spoken in clinical practice. The orthographic appearance of the proposed name is evaluated using a number of different handwriting samples. DMEPA applies expertise gained from root-cause analysis of postmarketing 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).

[3] 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/Similar shape Upstrokes Down strokes Cross-strokes 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, DMEPA 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 searches 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. A standard description of the databases used in the searches is provided in the reference section of this review. To complement the process, the DMEPA uses 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, DMEPA reviews 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. DMEPA also evaluates if there are characteristics included in the composition that may render the name unacceptable from a safety perspective (abbreviation, dosing interval, etc.).

2. Expert Panel Discussion

DMEPA gathered CDER professional opinions on the safety of the proposed product and discussed the proposed proprietary name (Expert Panel Discussion). The Expert Panel is composed of Division of Medication Errors Prevention (DMEPA) staff and representatives from the Office of Prescription Drug Promotion (OPDP). We also consider input from other review disciplines (OND, ONDQA/OBP). 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 database and information searches to the Expert Panel for consideration. Based on the clinical and professional experiences of the Expert Panel members, the Panel may recommend additional 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 Simulation 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 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 record their interpretations of the orders which are recorded electronically.

4. Comments from Other Review Disciplines

DMEPA requests the Office of New Drugs (OND) and/or Office of Generic Drugs (OGD), ONDQA or OBP for their comments or concerns with the proposed proprietary name, ask for any clinical issues that may impact the DMEPA review during the initial phase of the name review. Additionally, when applicable, at the same time DMEPA requests concurrence/non-concurrence with OPDP's decision on the name. The primary Safety Evaluator addresses any comments or concerns in the safety evaluator's assessment.

The OND/OGD Regulatory Division is contacted a second time following our analysis of the proposed proprietary name. At this point, DMEPA conveys their decision to accept or reject the name. The OND or OGD Regulatory Division is requested to provide any further information that might inform DMEPA's final decision on the proposed name.

Additionally, other review disciplines opinions such as ONDQA or OBP may be considered depending on the proposed proprietary name.

5. Safety Evaluator Risk Assessment of the Proposed Proprietary Name

The primary Safety Evaluator applies his/her individual expertise gained from evaluating medication errors reported to FDA, considers all aspects of the name that may be misleading or confusing, conducts a Failure Mode and Effects Analysis, and provides an overall decision on acceptability dependent on their 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.[4] 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

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

characteristics listed in Section 1.2 of this review. 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? And are there any components of the name that may function as a source of error beyond sound/look-alike?"***

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 or because of some other component of the name. 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.

Moreover, 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 Overall Risk Assessment:

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

b. DMEPA identifies that the proposed proprietary name is misleading because of similarity in spelling or pronunciation to another proprietary or established name of a different drug or ingredient [CFR 201.10.(C)(5)].

c. FMEA identifies the potential for confusion between the proposed proprietary name and other proprietary or established drug name(s), and demonstrates that medication errors are likely to result from the drug name confusion under the conditions of usual clinical practice.

d. The proposed proprietary name contains an USAN (United States Adopted Names) stem.

e. DMEPA identifies a potential source of medication error within the proposed proprietary name. For example, the proprietary name may be misleading or, inadvertently, introduce ambiguity and confusion that leads to errors. Such errors may not necessarily involve confusion between the proposed drug and another drug product but involve a naming characteristic that when incorporated into a proprietary name, may be confusing, misleading, cause or contribute to medication errors.

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 generally recommends that the Sponsor select an alternative proprietary name and submit the alternate name to the Agency for 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 Sponsor 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/Sponsor. However, the safety concerns set forth in criteria a through e above are supported either by FDA regulation or by external healthcare authorities, including the Institute of Medicine (IOM), World Health Organization (WHO), the Joint Commission, and the Institute for Safe Medication Practices (ISMP). These organizations have examined medication errors resulting from look- or sound-alike drug names, confusing, or misleading 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 preventable source of medication error that, in many instances, the Agency and/or Sponsor 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. Sponsors have undertaken higher-leverage strategies, such as drug name changes, in the

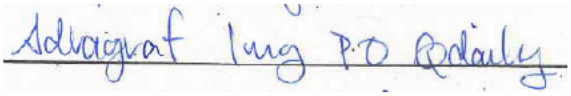
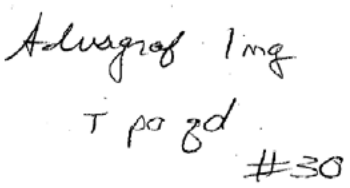
past but at great financial cost to the Sponsor and at the expense of the public welfare, not to mention the Agency's credibility as the authority responsible for approving the error-prone proprietary name. Moreover, even after Sponsors' have changed a product's proprietary name in the post-approval 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.

Appendix B: Letters with Possible Orthographic or Phonetic Misinterpretation

Letters in Name, Advagraf	Scripted May Appear as	Spoken May Be Interpreted as
Capital "A"	ce, FL, H, s	Any vowel
Lower case "a'	el, ci, cl, d, o, u	Any vowel
'Ad'	At, Slu	
Lower case 'd'	cl	'b', 't'
Lower case 'v'	e, l, r, u	'f', 'm', 'r'
Lower case 'g'	q, j, s	'k', 'j'
Lower case 'r'	e, I, l, n, s, v	
Lower case 'f'	t	'pf', 'ph'

Appendix C: Prescription Simulation Samples and Results

Figure 1. Advagraf Study (Conducted on June 5, 2012)

Handwritten Requisition Medication Order	Verbal Prescription
Medication Order: 	Advagraf 1 mg orally daily
Outpatient Prescription: 	

FDA Prescription Simulation Responses (Aggregate 1 Rx Studies Report)

Study Name: Advagraf

As of Date 7/2/2012

84 People Received Study

28 People Responded

Total	11	6	11	28
INTERPRETATION	**INPATIENT**	**VOICE**	**OUTPATIENT**	**TOTAL**
ABDIGRAF	0	1	0	1
ADEAGRAF	1	0	0	1
ADLAGRAF	5	0	0	5
ADMOGRAF	0	1	0	1
ADOGRAF	0	1	0	1
ADRAGRAF	2	0	0	2
ADREGRAFT	0	1	0	1
ADVAGRAF	3	0	7	10
ADVAGROF	0	0	1	1
ADVIGRAF	0	2	0	2
ADVOGROF	0	0	1	1
ATVAGRAF	0	0	1	1
SLUVAGRAF	0	0	1	1

Appendix D: Proprietary names not likely to be confused or not used in usual practice settings for the reasons described. (n=11)

No.	Proprietary Name	Active Ingredient	Similarity to Advagraf	Failure preventions
1	Accupril	Quinapril HCl	Look Alike	The pair has sufficient orthographic differences
2	Adipoxil	Vitamin B5/Green Tea/Guarana Extract (caffeine)/Citrus Aurantium (synephrine) plus other herbal supplements	Look Alike	This is a natural supplement that has been discontinued due to the ingredient synephrine. Products with ephedra were removed from the US market due to safety concerns.
3	N/A	Alprazolam	Look Alike	The pair has sufficient orthographic differences
4	N/A	Anastrozole	Look Alike	The pair has sufficient orthographic differences
5	Androderm	Testosterone	Look Alike	The pair has sufficient orthographic differences
6	Atripla	Efavirenz/Emtricitabine/ Tenofovir disoproxil fumarate	Look Alike	The pair has sufficient orthographic differences
7	N/A	Atropine Sulfate	Look Alike	The pair has sufficient orthographic differences
8	Avapro	Irbesartan	Look Alike	The pair has sufficient orthographic differences
9	Advil	Ibuprofen	Look & Sound Alike	The pair has sufficient orthographic and phonetic differences
10	Avandia	Rosiglitazone Maleate	Look & Sound Alike	The pair has sufficient orthographic and phonetic differences
11	Viagra	Sildenafil Citrate	Look & Sound Alike	The pair has sufficient orthographic and phonetic differences

Appendix E: Risk of medication errors due to product confusion minimized by dissimilarity of the names and/ or use in clinical practice for the reasons described. (n=15)

No.	**Proposed name: Advagraf** **Dosage Form:** Extended-Release Capsule **Strengths:** 0.5 mg, 1 mg, 5 mg **Usual Dose:** (b) (4)	**Failure Mode: Incorrect Product Ordered/ Selected/Dispensed or Administered because of Name confusion** **Causes (could be multiple)**	**Prevention of Failure Mode** **In the conditions outlined below, the following combination of factors, are expected to minimize the risk of confusion between these two names**
1	Adagen (Pegademase Bovine) Injection Solution **Strength:** 250 Unit/mL **Usual Dose:** Inject intramuscularly every 7 days; 10 units/kg for the 1st dose, 15 units/kg for the 2nd dose, 20 units/kg for the 3rd dose. For example, a child weighing 34 kg would receive a dose of 340 units (1.36 mL) for the 1st dose, 510 units (2.04 mL) for the 2nd dose and 680 units (2.72 mL) for the 3rd dose. Maintenance Dose: 20 units/kg/week. For example, a child weighing 34 kg would receive 680 units/week (2.72 mL/week). Maximum Dose: 30 units/kg as a single dose. For example, a child weighing 34 kg would receive 1020 units (4.08 mL).	**Orthographic Similarity:** Both names begin with the letters 'Ad' and contain a downstroke 'g' in the infix of their names.	**Orthographic Difference:** Advagraf contains the letters 'va' in the infix of the name vs. 'a' in Adagen giving the infix of Advagraf a longer appearance. Also, Advagraf contains a potential upstroke or downstroke 'f' at the end of name giving the names a different shape and appearance when scripted. **Differentiating Product Characteristics:** Strength or Dose: No strength or dose overlap. Advagraf is available in multiple strengths; thus, a strength or dose (XX mg) would need to be specified on the prescription for dispensing. Frequency: Every 7 days vs. once daily Dose and Unit of measure: Adagen is dosed as XX Units or mL vs. XX capsule(s) or XX mg

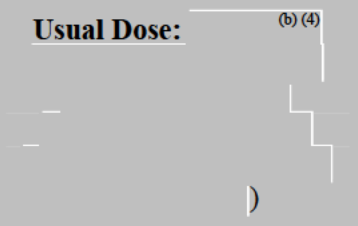
No.	Proposed name: Advagraf **Dosage Form:** Extended-Release Capsule **Strengths:** 0.5 mg, 1 mg, 5 mg **Usual Dose:** (b) (4))	Failure Mode: Incorrect Product Ordered/ Selected/Dispensed or Administered because of Name confusion **Causes (could be multiple)**	Prevention of Failure Mode **In the conditions outlined below, the following combination of factors, are expected to minimize the risk of confusion between these two names**
2	Adipex-P (Phentermine HCl) Tablet, Capsule **Strength:** 37.5 mg **Usual Dose:** One capsule or tablet by mouth once daily	**Orthographic Similarity:** Both names begin with the letters 'Ad' and contain a downstroke in the infix of their names. **Route of Administration:** Both are given orally. **Frequency:** Both may be prescribed once daily.	**Orthographic Difference:** Advagraf contains the letters 'va' in the infix of the name vs. 'i' in Adipex giving the infix of Advagraf a longer appearance. Also, Advagraf contains a potential upstroke or downstroke 'f' at the end of the name giving the names a different shape and appearance when scripted. **Differentiating Product Characteristics:** Strength or Dose: No strength or dose overlap. Advagraf is available in multiple strengths; thus, a strength or dose (XX mg) would need to be specified on the prescription for dispensing.
3	Adroyd (Oxymetholone) Tablet **Strengths:** 5 mg, 10 mg **Usual Dose:** 1 mg/kg/day to 5 mg/kg/day by mouth. A patient weighing 75 kg would receive 75 mg/day to 375 mg/day. Unable to find frequency of administration information in commonly used drug databases.	**Orthographic Similarity:** Both names begin with the letters 'Ad', contain a downstroke in the 5th position and an upstroke at the end of their names. **Strength:** Strength overlap. Both products are available in 5 mg. Numeric strength overlap (1 mg vs. 10 mg) **Route of Administration:** Both are given orally.	**Orthographic Difference:** The suffix 'graf' in Advagraf contains the letters 'ra' between the downstroke 'g' and if 'f' is scripted as an upstroke, upstroke 'f', which when scripted appears longer than the suffix 'yd' in Adroyd.

No.	Proposed name: Advagraf **Dosage Form:** Extended-Release Capsule **Strengths:** 0.5 mg, 1 mg, 5 mg **Usual Dose:** (b) (4)	Failure Mode: Incorrect Product Ordered/ Selected/Dispensed or Administered because of Name confusion Causes (could be multiple)	Prevention of Failure Mode In the conditions outlined below, the following combination of factors, are expected to minimize the risk of confusion between these two names
4	Adrucil (Fluorouracil) Injection Solution **Strengths:** 2.5 gm/50 mL, 5 gm/100 mL, 500 mg/10 mL (50 mg/mL) **Usual Dose:** Initial Dose: 12 mg/kg once daily by intravenous bolus for 4 successive days. 6 mg/kg on days 6, 8, 10, 12. No therapy on days 5, 7, 9, 11. For example, a patient weighing 75 kg would receive 900 mg (18 mL) for 4 days, then 450 mg (9 mL) on days 6, 8, 10, 12. Maintenance Dose: 10 mg/kg/week to 15 mg/kg/week as a single dose. For example, a patient weighing 75 kg would receive 750 mg (15 mL) to 1,125 mg (22.5 mL). Maximum dose: 800 mg/day or 1,000 mg/week	**Orthographic Similarity:** Both names begin with the letters 'Ad' and contain an upstroke at the end of their names. **Dose:** Numeric dose overlap is possible with the various dosing ranges for both products based on the patient's weight (XX mL vs. XX mg). **Frequency:** Both may be prescribed once daily.	**Orthographic Difference:** Advagraf contains a downstroke 'g' in the 5th position of the name which is not seen in Adrucil giving the names a different shape and appearance. When scripted, the suffix 'graf' in Advagraf appears longer than the suffix 'cil' in Adrucil.

No.	Proposed name: Advagraf **Dosage Form:** Extended-Release Capsule **Strengths:** 0.5 mg, 1 mg, 5 mg **Usual Dose:** (b) (4))	Failure Mode: Incorrect Product Ordered/ Selected/Dispensed or Administered because of Name confusion **Causes (could be multiple)**	**Prevention of Failure Mode** **In the conditions outlined below, the following combination of factors, are expected to minimize the risk of confusion between these two names**
5	AdvaCAL 1000 (Calcium hydroxide/Calcium oxide/Vitamin D3) Capsule **Strength:** 500 mg **Usual Dose:** 3 capsules by mouth twice a day AdvaCAL Ultra 1000 (Calcium hydroxide/Calcium oxide/Multivitamins & Minerals) **Strength:** 500 mg **Usual Dose:** 3 capsules by mouth twice a day AdvaCAL Intensive (Calcium hydroxide/Calcium oxide/Vitamin D3/Zinc/Copper/Manganese) **Strength:** 600 mg **Usual Dose:** 3 capsules by mouth twice a day	**Orthographic Similarity:** Both names begin with an identical letter string 'Adva' and contain an upstroke at the end of their names. **Route of Administration:** Both are given orally.	**Orthographic Difference:** Advagraf contains a downstroke 'g' in the 5th position of the name followed by the letters 'ra' giving the names a different shape and a longer appearance than Advacal when scripted. **Differentiating Product Characteristics:** Modifier: Advacal is the root name for 3 different product lines; therefore, a modifier would need to be specified in order for the correct product to be dispensed. Strength: No strength overlap. Advagraf is available in multiple strengths; thus, a strength would need to be specified on the prescription for dispensing. Frequency: Twice daily vs. once daily

No.	Proposed name: Advagraf **Dosage Form:** Extended-Release Capsule **Strengths:** 0.5 mg, 1 mg, 5 mg **Usual Dose:** (b) (4)	Failure Mode: Incorrect Product Ordered/ Selected/Dispensed or Administered because of Name confusion Causes (could be multiple)	Prevention of Failure Mode In the conditions outlined below, the following combination of factors, are expected to minimize the risk of confusion between these two names
6	Advate (Antihemophilic factor, recombinant) Injection Powder for Solution **Strengths:** 250 Units, 500 Units, 1000 Units, 1500 Units, 2000 Units, 3000 Units **Usual Dose:** A dose of rAHF sufficient to achieve a level of 20% to 100% of normal should be given intravenously based on the indication. Infusions every 8 to 24 hours. For example to achieve a level of 20% of normal. A child weighing 15 kg would receive 150 units and an adult weighing 75 kg would receive 750 units.	**Orthographic Similarity:** Both names begin with the identical letter string 'Adva'.	**Orthographic Difference:** Advagraf contains a downstroke 'g' in the 5th position and a potential upstroke 'f' in the 8th position of the name while Advate contains a cross-stroke 't' in the 5th position of the name, therefore giving the name Advagraf a different shape and longer appearance when scripted. **Differentiating Product Characteristics:** Dose and Unit of measure: No dose overlap. Advate is dosed as XX units/dL vs. XX capsule(s) or XX mg.

No.	Proposed name: Advagraf **Dosage Form:** Extended-Release Capsule **Strengths:** 0.5 mg, 1 mg, 5 mg **Usual Dose:** (b) (4)	Failure Mode: Incorrect Product Ordered/ Selected/Dispensed or Administered because of Name confusion Causes (could be multiple)	Prevention of Failure Mode **In the conditions outlined below, the following combination of factors, are expected to minimize the risk of confusion between these two names**
7	Advicor (Niacin/Lovastatin) Extended-Release Capsule **Strengths:** 500 mg/20 mg, 750 mg/20 mg, 1000 mg/20 mg, 1000 mg/40 mg **Usual Dose:** 500 mg/20 mg to 2000 mg/40 mg by mouth once daily at bedtime	**Orthographic Similarity:** Both names begin with an identical letter string 'Adv'. **Dose:** Both may be written as one dose without specifying the dosage form. **Route of Administration:** Both are given orally. **Frequency:** Both may be prescribed once daily.	**Orthographic Difference:** Advagraf contains a downstroke 'g' in the 5th position and a potential upstroke 'f' in the 8th position of the name which is not seen in Advicor giving the names a different shape and appearance when scripted. **Differentiating Product Characteristics:** Strength: No strength overlap. Advagraf and Advicor are available in multiple strengths; thus, a strength would need to be specified on the prescription for dispensing of both products.

No.	Proposed name: Advagraf **Dosage Form:** Extended-Release Capsule **Strengths:** 0.5 mg, 1 mg, 5 mg **Usual Dose:** (b) (4) 	Failure Mode: Incorrect Product Ordered/ Selected/Dispensed or Administered because of Name confusion Causes (could be multiple)	Prevention of Failure Mode In the conditions outlined below, the following combination of factors, are expected to minimize the risk of confusion between these two names
8	Androgel (Testosterone) Transdermal Gel Packets **Strengths:** 25 mg/2.5 gm, 50 mg/5 gm **Usual Dose:** 5 gm (50 mg) to 10 gm (100 mg) applied once daily in the morning to shoulders and/or upper arms or abdomen Androgel Pump (Testosterone) Transdermal Gel **Strength:** 1.25 gm/Actuation (1%), 20.25 mg/Actuation (1.62%) **Usual Dose:** Apply 20.25 mg (1 pump) to 81 mg (4 pumps) topically once daily in the morning to the shoulders and upper arms	**Orthographic Similarity:** Both names contain 8 letters, begin with the letter 'A', contain an upstroke 'd' in the prefix, a downstroke 'g' in the infix, and an upstroke at the end of their names. **Strength:** Numeric strength overlap. (5 gm vs. 5 mg & 1% vs. 1 mg) **Dose:** Both may be written as one dose without specifying the dosage form. **Frequency:** Both may be prescribed once daily.	**Orthographic Difference:** Androgel contains the letter 'n' in the prefix of the name ('And') giving the prefix a longer appearance than the prefix in Advagraf ('Ad'). Also, Advagraf contains the letter string 'ra' in the suffix ('graf') vs. 'e' in Androgel ('gel') giving the suffix of Advagraf a longer appearance when scripted. **Differentiating Product Characteristics:** Dosage Form: Packet or Pump vs. Capsule

No.	Proposed name: Advagraf **Dosage Form:** Extended-Release Capsule **Strengths:** 0.5 mg, 1 mg, 5 mg **Usual Dose:** (b)(4)	Failure Mode: Incorrect Product Ordered/ Selected/Dispensed or Administered because of Name confusion Causes (could be multiple)	Prevention of Failure Mode In the conditions outlined below, the following combination of factors, are expected to minimize the risk of confusion between these two names
9	Avandaryl (Rosiglitazone/Glimepiride) Tablet **Strength:** 4 mg/1 mg, 4 mg/2 mg, 4 mg/4 mg, 8 mg/2 mg, 8 mg/4 mg **Usual Dose:** 4 mg/1 mg to 8 mg/4 mg by mouth once daily with the first meal of the day	**Orthographic Similarity:** Both names begin with the letter 'A'. and end with an upstroke. **Route of Administration:** Both are given orally. **Dose:** Both may be written as one dose without specifying the dosage form. **Frequency:** Both may be prescribed once daily.	**Orthographic Difference:** Advagraf contains an upstroke 'd' in the 2nd position and a downstroke 'g' in the 5th position while Avandaryl contains an upstroke 'd' in the 5th position and a downstroke 'y' in the 8th of the name giving both names a different shape and appearance when scripted. **Differentiating Product Characteristics:** Strength: No strength overlap. Advagraf and Avandaryl are available in multiple strengths; thus, a strength would need to be specified on the prescription for dispensing of both products.

No.	Proposed name: Advagraf **Dosage Form:** Extended-Release Capsule **Strengths:** 0.5 mg, 1 mg, 5 mg **Usual Dose:** (b) (4)	Failure Mode: Incorrect Product Ordered/ Selected/Dispensed or Administered because of Name confusion Causes (could be multiple)	Prevention of Failure Mode In the conditions outlined below, the following combination of factors, are expected to minimize the risk of confusion between these two names
10	Ciclopirox (Ciclopirox) External Solution, Kit **Strength:** 8% **Usual Dose:** Apply once daily to all affected nails Ciclopirox (Ciclopirox) Gel **Strength:** 0.77% **Usual Dose:** Apply to affected areas twice daily for 4 weeks Ciclopirox (Ciclopirox) Shampoo **Strength:** 1% **Usual Dose:** Wet hair and apply approximately 5 mL to 10 mL to scalp. Lather and leave on for 3 minutes. Rinse off.	**Orthographic Similarity:** Both names begin with similar letters (Cicl vs. Ad). **Strength:** Numeric strength overlap. (1% vs. 1 mg) **Frequency:** Both may be prescribed once daily.	**Orthographic Difference:** Advagraf contains a downstroke 'g' in the 5th position and the letters 'ra' in the suffix vs. Ciclopirox contains a downstroke 'p' in the 6th position and the letters 'iro' in the suffix giving the suffix of Ciclopirox a longer appearance when scripted. **Differentiating Product Characteristics:** Dosage Form: Kit or Solution or Gel or Shampoo vs. Capsule

No.	Proposed name: Advagraf **Dosage Form:** Extended-Release Capsule **Strengths:** 0.5 mg, 1 mg, 5 mg **Usual Dose:** (b) (4)	Failure Mode: Incorrect Product Ordered/ Selected/Dispensed or Administered because of Name confusion Causes (could be multiple)	Prevention of Failure Mode In the conditions outlined below, the following combination of factors, are expected to minimize the risk of confusion between these two names
11	Colazal (Balsalazide Disodium) Capsule **Strength:** 750 mg **Usual Dose:** 750 mg (1 capsule) or 2,250 mg (3 capsules) by mouth 3 times daily for up to 8 weeks	**Orthographic Similarity:** Both names begin with an orthographically similar letter string 'Col' vs. 'Ad' and contains a potential downstroke 'z' vs. 'g' and a potential upstroke 'l' vs. 'f' in the last position when scripted. **Route of Administration:** Both are given orally. **Dose:** Both may be written as one dose without specifying the dosage form.	**Orthographic Difference:** Advagraf contains the letters 'va' in the infix and the letters 'ra' in the suffix vs. Colazal contains the letter 'a' in the infix and in the suffix giving the infix and suffix of Advagraf a longer appearance when scripted. **Differentiating Product Characteristics:** Strength: No strength overlap. Advagraf is available in multiple strengths; thus, a strength would need to be specified on the prescription for dispensing. Frequency: Three times daily vs. once daily

No.	Proposed name: Advagraf **Dosage Form:** Extended-Release Capsule **Strengths:** 0.5 mg, 1 mg, 5 mg **Usual Dose:** (b) (4)	Failure Mode: Incorrect Product Ordered/ Selected/Dispensed or Administered because of Name confusion Causes (could be multiple)	Prevention of Failure Mode In the conditions outlined below, the following combination of factors, are expected to minimize the risk of confusion between these two names
12	Gengraf (Cyclosporine Modified) Capsule **Strength:** 25 mg, 100 mg Gengraf (Cyclosporine Modified) Solution **Strength:** 100 mg/mL **Usual Dose:** 2.5 mg/kg/day to 12 mg/kg/day taken twice daily as a divided dose. For example, a patient weighing 75 kg would receive approximately 100 mg to 450 mg twice daily.	**Orthographic Similarity:** Both names end with the identical letter string 'graf'. **Route of Administration:** Both are given orally. **Dose:** Both may be written as one dose without specifying the dosage form.	**Orthographic Difference:** The letter strings in the prefix of both names (Gen vs. Adva) are not orthographically similar. Also, Advagraf contains an upstroke 'd' in the 2nd position which is not seen in Gengraf giving the names a different shape and appearance when written. **Differentiating Product Characteristics:** Strength: No strength overlap. Advagraf is available in multiple strengths; thus, a strength would need to be specified on the prescription for dispensing of both products. Frequency: Twice daily vs. once daily
13	Advair Diskus (Fluticasone Propionate/Salmeterol) Powder for Inhalation **Strengths:** 100 mcg/50 mcg, 250 mcg/50 mcg, 500 mcg/50 mcg **Usual Dose:** 1 inhalation twice daily Advair HFA (Fluticasone Propionate/Salmeterol) Inhalation Aerosol **Strengths:** 45 mcg/21 mcg, 115 mcg/21 mcg, 230 mcg/21 mcg **Usual Dose:** 2 inhalations twice daily	**Orthographic and Phonetic Similarities:** Both names begin with the identical letter string 'Adva'. When spoken, the first syllable in each name sounds identical ('Ad' vs. 'Ad').	**Orthographic and Phonetic Differences:** Advagraf contains 8 letters, a downstroke 'g' in the 5th position and a potential downstroke or upstroke 'f' in the 8th position of the name which are not seen in the root name Advair which contains 6 letters giving both names a different shape and the name Advagraf a longer appearance when scripted. Advair contains 2 syllables vs. 3 syllables in Advagraf and when spoken, the 2nd syllable in both names sound distinctly different ('vair' vs. 'va'). **Differentiating Product Characteristics:** Strength: No strength overlap. Advagraf, Advair Diskus and Advair HFA are available in multiple strengths; thus, a strength would need to be specified on the prescription for dispensing of both products.

No.	Proposed name: Advagraf **Dosage Form:** Extended-Release Capsule **Strengths:** 0.5 mg, 1 mg, 5 mg **Usual Dose:** (b) (4))	Failure Mode: Incorrect Product Ordered/ Selected/Dispensed or Administered because of Name confusion Causes (could be multiple)	Prevention of Failure Mode In the conditions outlined below, the following combination of factors, are expected to minimize the risk of confusion between these two names
14	Avodart (Dutasteride) Capsule **Strength:** 0.5 mg **Usual Dose:** One capsule by mouth once daily	**Orthographic and Phonetic Similarities:** Both names begin with the letter 'A'. Both names contain 3 syllables and when spoken, the first 2 syllables sound similar when the stress is not placed on the letter 'd' in Advagraf ('Avo' vs. 'Adva'). **Strength:** Strength overlap. Both products are available in 0.5 mg. **Dosage Form:** Both are capsules. **Route of Administration:** Both are given orally. **Dose:** Both may be written as one dose without specifying the dosage form. **Frequency:** Both may be prescribed once daily.	**Orthographic and Phonetic Differences:** Advagraf contains an upstroke 'd' in the 2nd position and a downstroke 'g' in the 5th position while Avodart contains an upstroke 'd' in the 4th position of the name giving both names a different shape and appearance when scripted. When spoken, the 2nd syllable in both names sound distinctly different ('graf' vs. 'dart').

No.	Proposed name: Advagraf **Dosage Form:** Extended-Release Capsule **Strengths:** 0.5 mg, 1 mg, 5 mg **Usual Dose:** (b) (4)	Failure Mode: Incorrect Product Ordered/ Selected/Dispensed or Administered because of Name confusion Causes (could be multiple)	Prevention of Failure Mode In the conditions outlined below, the following combination of factors, are expected to minimize the risk of confusion between these two names
15	Prograf (Tacrolimus) Capsule **Strength:** 0.5 mg, 1 mg, 5 mg **Usual Dose:** Heart Transplant: 0.75 mg/kg/day by mouth in 2 divided doses every 12 hours. For example, a patient weighing 75 kg would receive approximately 28 mg twice daily. Kidney Transplant: 0.2 mg/kg/day by mouth in combination with azathioprine or 0.1 mg/kg/day in combination with mycophenolate mofetil and interleukin-2 receptor antagonist every 12 hours. For example, a patient weighing 75 kg would receive 3.75 mg to 7.5 mg twice daily. Liver Transplant: 0.1 mg/kg/day to 0.2 mg/kg/day by mouth every 12 hours. For example a child weighing 15 kg would receive 0.75 mg to 1.5 mg twice daily.	**Orthographic and Phonetic Similarities:** Both names end with the identical letter string 'graf'. When spoken, the last syllable in both names sound identical ('graf' vs. 'graf'). **Strength:** Strength overlap. Both products are available in 0.5 mg, 1 mg and 5 mg. **Dosage Form:** Both are capsules. **Route of Administration:** Both are given orally.	**Orthographic and Phonetic Differences:** The letter strings in the prefix of both names (Pro vs. Adva) are not orthographically similar. Also, Advagraf contains an upstroke 'd' in the 2nd position which is not seen in Prograf giving the names a different shape and appearance when written. Prograf contains 2 syllables vs. Advagraf contains 3 syllables. When spoken, the first 2 syllables in the name Advagraf sound distinctly different than the first syllable in Prograf ('Adva' vs. Pro).

Appendix F:

Foreign Names for Tacrolimus Extended-Release Products:

Table 1 Foreign Names for Tacrolimus Products

Name	Number of Approved Countries
Advagraf	50
Prograf XL	17 (Latin America, New Zealand, Australia)
Graceptor	1 (Japan)
Tacrolimus sustained-release capsules	1 (China)
Total	**69**

Source: Data on file at Astellas.

Foreign Names for Immediate-Release Tacrolimus Products in the European Region:

Table 2 Tacrolimus Products Currently Marketed in the European Region

Country	License Holder/ Applicant	Product name	Registration Date
Austria	Sandoz	Tacrolimus	1/28/2010
Austria	Teva	Tacni	12/13/2010
Belgium	Sandoz	Tacrolimus	12/21/2009
Bulgaria	Teva	Tacni	10/20/2010
Denmark	Sandoz	Tacrolimus	1/26/2010
Finland	Accord Healthcare Ltd.	Tacrolimus	2/18/2011
Finland	Sandoz A/S	Tacrolimus	1/20/2010
Finland	Teva Sweden AB	Tacni	1/17/2011
Germany	Accord	Tacrolimus	1/17/2011
Germany	CellPharm	TACRO-cell	1/17/2011
Germany	Dexcel	Vivadex	2/21/2011
Germany	Hexal	Tacrolimus	2/10/2010
Germany	Panacea	Tacpan	6/9/2011
Germany	Teva	Tacni	11/24/2011
Great Britain	Dexcel	Vivadex	10/26/2010
Great Britain	Sandoz	Adoport	1/14/2010
Great Britain	Teva	Tacni	10/26/2010
Hungary	Mylan	Tacrolimus	4/27/2011
Hungary	Sandoz	Tacrolimus	3/22/2011
Italy	Accord	Tacrolimus	4/8/2011
Italy	Crinos Spa	Aletris	6/22/2011
Italy	Mylan	Tacrolimus	9/28/2011
Italy	Teva	Tacni	5/3/2011
Malta	Accord	Tacrolimus	8/12/2010
Malta	Arrow Generics Ltd	Takon	9/24/2010
Netherlands	Accord	Tacrolimus	9/21/2010
Netherlands	PharOs	Tacni	12/21/2010
Netherlands	Sandoz	Tacrolimus	11/22/2009
Norway	Sandoz A/S	Tacrolimus	1/1/2011

Table continued on next page

Country	License Holder/ Applicant	Product name	Registration Date
Norway	Teva	Tacni	1/7/2011
Poland	ICN Polfa	Taliximun	1/20/2011
Poland	Intas	Tacrolimus	6/1/2011
Poland	Sandoz	Cidimus	5/21/2010
Poland	Teva	Tacni	12/2/2010
Portugal	Generis	Tacrolimus	4/28/2011
Portugal	Sandoz	Tacrolimus	12/17/2009
Portugal	Teva	Tacni	9/17/2010
Slovakia	Other	Gecrol	11/23/2010
Slovakia	Sandoz	Tacrolimus	1/28/2010
Slovenia	Teva	Tacni	5/20/2011
Spain	Accord	Tacrolimus	10/13/2010
Spain	Laboratorios Juste, S.A.	Tartrime	11/18/2011
Spain	Mylan	Other	2/4/2011
Spain	Sandoz	Tacrolimus	3/17/2011
Spain	Stada	Other	3/28/2011
Sweden	Accord Healthcare Ltd.	Tacrolimus	10/22/2010
Sweden	Sandoz A/S	Tacrolimus	3/26/2010
Sweden	Teva Sweden AB	Tacni	12/16/2010
Switzerland	Actavis	Tacrolimus	7/22/2010
Switzerland	Sandoz	Tacrolimus	9/3/2009
Switzerland	Teva	Tacrolimus	4/15/2011

Note: Brand names and respective countries where tacrolimus products are registered but not yet marketed in Europe are not included in this table.

Source: Data on file at Astellas.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

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11/19/2012

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