CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022472Orig1s000

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:	June 26, 2014
Reviewer:	Sarah K. Vee, PharmD Division of Medication Prevention and Analysis
Team Leader	Yelena Maslov, PharmD Division of Medication Prevention and Analysis
Drug Name and Strengths:	Afrezza (insulin human [rDNA origin]) Inhalation Powder 4 units and 8 units per cartridge
Application Type/Number:	NDA 205649
Applicant/sponsor:	Astra Zeneca and Bristol-Myers Squibb
OSE RCM #:	2013-2356-1

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

CONTENTS

1 INTRODUCTION

This review is a re-assessment of the proposed proprietary name, Afrezza, which DMEPA found acceptable in OSE Review #2013-2356, dated January 13, 2013 under NDA 205649. We are re-reviewing the proposed proprietary name due to changes in product characteristics (i.e. strengths).

2 METHODS AND DISCUSSION

We note that the proposed product characteristics were altered (i.e. strengths). Thus, we evaluated the previously identified names of concern considering any lessons learned from recent post-marketing experience, which did not alter our previous conclusion regarding the acceptability of the proposed proprietary name.

3 CONCLUSIONS

The re-evaluation of the proposed proprietary name, Afrezza, did not identify any vulnerabilities that would result in medication errors with the change in the strengths. Thus, DMEPA has no objection to the proprietary name, Afrezza, for this product at this time.

If you have further questions or need clarifications, please contact Canida Lyle, OSE project manager, at 301-796-1637.

3.1 COMMENTS TO THE APPLICANT

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

4 REFERENCES

1. OSE Reviews 2013-2356 Afrezza (Insulin Human[rDNA origin]) Proprietary Name Review [Acceptable], Sarah K. Vee, PharmD, January 13, 2013.

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

/s/

SARAH K VEE
06/26/2014

YELENA L MASLOV
06/26/2014

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:	January 13, 2014
Reviewer:	Sarah K. Vee, PharmD Division of Medication Prevention and Analysis
Team Leader:	Yelena Maslov, PharmD Division of Medication Prevention and Analysis
Drug Name and Strength:	Afrezza (insulin human [rDNA origin]) Inhalation Powder 3 units and 6 units per cartridge
Application Type/Number:	NDA 22472
Applicant/Sponsor:	MannKind
OSE RCM #:	2013-2356

*** 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, Afrezza, 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

Afrezza Inhalation Powder is a 505 (b)(1) application under NDA 022472 originally submitted to the FDA on March 16, 2009.

Table 1: Regulatory Correspondence Dates

Date	Synopsis
March 16, 2009	NDA 022472 originally submitted
December 8, 2009	DMEPA initially reviewed the name, Afrezza, and found it acceptable, based on the provided product characteristics, on December 8, 2009 in OSE Review #2009-1471.
March 12, 2010	Complete Response (CR)
June 29, 2010	Applicant submitted a proprietary name request for Afrezza and [redacted] (b) (4) for the product, which DMEPA found unacceptable.
August 27, 2010	The Applicant submitted a proprietary name withdrawal request for the name Afrezza and [redacted] (b) (4)
December 9, 2010	Afrezza was reviewed again in OSE Review# 2010-1578 and was found acceptable
January 18, 2011	Second complete response
October 11, 2013	Response to second CR

1.2 PRODUCT INFORMATION

The following product information is provided in the October 17, 2013 proprietary name submission.

- Active Ingredient: insulin human [rDNA origin]
- Indication of Use: ultra rapid acting insulin to improve glycemic control in adults with type 1 or type 2 diabetes mellitus
- Route of Administration: oral inhalation
- Dosage Form: powder for inhalation
- Strength: 3 units and 6 units per cartridge

- Dose and Frequency: Individualized dosing taken before a meal or within 20 minutes after starting a meal
- How Supplied:

AFREZZA (insulin human [rDNA origin]) Inhalation Powder is available as 3 unit and 6 unit single-use cartridges. Three cartridges are contained in a single cavity of a blister strip. Each card contains 5 blister strips separated by perforations for a total of 15 cartridges. For convenience, the perforation allows users to remove a single strip containing 3 cartridges. Two cards of the same cartridge strength are packaged in a foil laminate overwrap (30 cartridges per foil package).

The cartridges are color-coded, blue for 3 units and green for 6 units. Each cartridge is marked with "*afrezza*" and "3 units" or "6 units".

The AFREZZA Inhaler is individually packaged in a translucent overwrap. The inhaler is fully assembled with a removable mouthpiece cover. The AFREZZA Inhaler can be used for up to 15 days from the date of first use. After 15 days of use, the inhaler must be discarded and replaced with a new inhaler.

AFREZZA is available in the following configurations:

- NDC (<47918-XXX-XX>), AFREZZA (insulin human [rDNA origin]) Inhalation Powder: 60 – 3 unit cartridges and 2 inhalers
- NDC (<47918-XXX-XX>), AFREZZA (insulin human [rDNA origin]) Inhalation Powder: 90 – 3 unit cartridges and 2 inhalers
- NDC (<47918-XXX-XX>), AFREZZA (insulin human [rDNA origin]) Inhalation Powder: 90 – 6 unit cartridges and 2 inhalers
- NDC (<47918-XXX-XX>), AFREZZA (insulin human [rDNA origin]) Inhalation Powder: 90 cartridges; 60 – 3 unit cartridges and 30 – 6 unit cartridges and 2 inhalers
- NDC (<47918-XXX-XX>), AFREZZA (insulin human [rDNA origin]) Inhalation Powder: 90 cartridges; 30 – 3 unit cartridges and 60 – 6 unit cartridges and 2 inhalers
- NDC (<47918-XXX-XX>), AFREZZA (insulin human [rDNA origin]) Inhalation Powder: 180 cartridges; 90 - 3 unit cartridges and 90 – 6 unit cartridges and 2 inhalers

- Storage:

Storage

Not in Use: Refrigerated Storage 2-8ºC (36-46ºF)

Sealed (Unopened) Foil Package	May be stored until the Expiration Date*

* If a foil package is not refrigerated, the contents must be used within 10 days.

In Use: Room Temperature Storage 25ºC (77ºF), excursions permitted 15-30 ºC (59-86 ºF)

Sealed (Unopened) Blister Cards + Strips	Must be used within 10 days
Opened Strips	Must be used within 3 days

Inhaler Storage:
Store at 2-25ºC (36-77ºF); excursions permitted. Inhaler may be stored refrigerated, but should be at room temperature before use.

Handling:
Before use, cartridges should be at room temperature for 10 minutes.

- Container and Closure Systems: The to-be-marketed Technosphere® Insulin (TI) Inhalation Powder / Gen2 Inhalation System includes single-use, color coded, pre-metered Cartridges that are manually placed into a re-useable, breath-powered, high resistance dry powder inhaler. Cartridges are packaged in blisters.

2 RESULTS

The following sections provide 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 Metabolism and Endocrinology Products (DMEP) concurred with the findings of OPDP's promotional assessment of the proposed name. The following aspects were considered in the safety evaluation of the name.

2.2 SAFETY ASSESSMENT

2.2.1 United States Adopted Names (USAN) SEARCH

The October 21, 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 Applicant indicated in their submission that the proposed name, Afrezza, has no derivation. This proprietary name is comprised of a single word that does not contain any components (i.e. a modifier, route of administration, dosage form, etc.) that are misleading or can contribute to medication error.

2.2.3 FDA Name Simulation Studies

We conducted two separate studies to assess the different interpretations for the letter string 'zz'. For the first study, the letter string 'zz' was written with down strokes whereas for the second study, it was scripted without the down strokes.

Sixty practitioners participated in DMEPA's first prescription studies. The interpretations did not overlap with any currently marketed products nor did the misinterpretations sound or look similar to any currently marketed products or any products in the pipeline. Twenty-two of the 60 participants responded correctly while ten voice participants responded with a single 'z' instead of the double 'zz'. The most common misinterpretation occurred with outpatient participants misinterpreting the letter string 'zz'. Variations include 'gz', 'yz', 'jy', and 'jz'. Seven of the inpatient participants misinterpreted the letter 'A' for 'S'.

Forty-four practitioners participated in DMEPA's second prescription studies. The interpretations did not overlap with any currently marketed products nor did the misinterpretations sound or look similar to any currently marketed products or any products in the pipeline. Thirty-three of the 45 participants responded correctly. The most common misinterpretation was with six voice participants where they responded with a single 'z'.

We have considered these variations in our look-alike and sound-alike searches and analysis (see Appendix B). Appendix C contains the results from the verbal and written prescription studies.

2.2.4 Comments from Other Review Disciplines at Initial Review

In response to the OSE, October 29, 2013 e-mail, DMEP did not forward any comments or concerns relating to the proposed proprietary name at the initial phase of the 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, Afrezza. Table 1 lists the names with orthographic, phonetic, or spelling similarity to the proposed proprietary name, Afrezza identified by the primary reviewer, the Expert Panel Discussion (EPD), and other review disciplines.

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

Name	*Source*	*Name*	*Source*	*Name*	*Source*
Abraxane	Previous review	Akurza	EPD/previous review	Apriso	Previous review
Abreva	EPD/previous review	Albenza	EPD/previous review	Arzerra	Previous review
(b) (4)	Previous review	Alenaze D	Previous review	Atarax	EPD
Afaxin	Previous review	Alesse 21 or 28	Previous review	Atralin	Previous review
(b) (4)	EPD	Allegra	Previous review	Atripla	Previous review
Afluria	EPD/previous review	Altafrin	EPD	Atuss DS	Previous review
Afrin & family	Previous review	Apidra	Previous review	Avinza	Previous review
Afrinol	Previous review	Aplenzin	Previous review	Cefizox	Previous review
Ofev***	EPD	Ofirmev	EPD	Oforta	Previous review
Sound Similar					
Name	*Source*	*Name*	*Source*	*Name*	*Source*
Alprazolam	EPD	Straterra	Previous review	Cyclessa	EPD/previous review
Look and Sound Similar					
Name	*Source*	*Name*	*Source*	*Name*	*Source*
Adrucil	Previous review	(b) (4) ***	Previous review	Iressa	EPD/previous review
Aflexa	EPD/previous review	Atreza	EPD/previous review		
Afresa***	EPD/previous review	Effexor	EPD		

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

Our analysis of the 37 names contained in Table 1 determined 37 names will not pose a risk for confusion as described in Appendices D through E.

2.2.6 Communication of DMEPA's Analysis at Midpoint of Review

DMEPA communicated our findings to the DMEP via e-mail on December 6, 2013. At that time we also requested additional information or concerns that could inform our review. Per e-mail correspondence from the DMEP on December 11, 2013, they stated no additional concerns with the proposed proprietary name, Afrezza.

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 Margarita Tossa, OSE project manager, at 301-796-4053.

3.1 COMMENTS TO THE APPLICANT

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

If any of the proposed product characteristics as stated in your October 17, 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. ***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.

10. ***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.

11. ***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.

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

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

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

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

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

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

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

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

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

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

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

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

18. 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.

19. 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.

---

[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 gathers gather 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, Afrezza	Scripted May Appear as	Spoken May Be Interpreted as
A	**Ce, Fl, H, O, S**	**Any vowel**
a	**el, ci, cl, d, o, u**	**Any vowel**
f	**b, d, l, p, t, g**	**Ph, v**
r	**c, e, n, s, v**	
e	**a, i, l, o, u, p**	**Any vowel**
z	**c, e, g, m, n, q, r, s, v, y**	**c, s, x**
Letter Strings		
re	**n, u, ir, er**	
zz	**u, r**	

Appendix C: Prescription Simulation Samples and Results

Figure 1. Afrezza Study (Conducted on 10/25/2013)

Handwritten Requisition Medication Order	Verbal Prescription
Medication Order: Afrezza 15 units before meals	Afrezza Use as directed 1 month supply

Outpatient Prescription:	
Afrezza UAD # 1 mo. supply	

FDA Prescription Simulation Responses (Aggregate 1 Rx Studies Report)

192 People
Received Study
60 People
Responded
Study Name: Afrezza

Total	**20**	**17**	**23**	
INTERPRETATION	**OUTPATIENT**	**VOICE**	**INPATIENT**	**TOTAL**
AFERGZA	1	0	0	1
AFIRYZA	1	0	0	1
AFRASA	0	1	0	1
AFREGZA	1	0	0	1
AFREJYA	1	0	0	1
AFRENZA	0	1	0	1
AFREZA	0	10	0	10
AFREZZA	2	4	16	22
AFRYZA	2	0	0	2
AFUGZA	5	0	0	5
AFUREJZA	1	0	0	1
AFUYZA	6	0	0	6
APHREZA	0	1	0	1
SFREZZA	0	0	7	7

Figure 2. Afrezza Study (Conducted on 11/01/2013)

Handwritten Requisition Medication Order	**Verbal Prescription**
Medication Order: Afrezza 15 units before meals	Afrezza use as directed 1 month supply

Outpatient Prescription:	
Afrezza Use as Directed 1 Month Supply	

192 People
Received Study
44 People
Responded
Study Name: Afrezza

Total	**18**	**11**	**15**	
INTERPRETATION	**OUTPATIENT**	**VOICE**	**INPATIENT**	**TOTAL**
AFNEZZA	0	0	1	1
AFRESSA	0	0	1	1
AFREZA	0	6	0	6
AFREZZA	17	5	11	33
AFREZZER	0	0	1	1
AGNEZZA 15 UNITS	0	0	1	1
SFREZZA	1	0	0	1

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

No.	Proprietary Name	Active Ingredient	Similarity to Afrezza	Failure preventions
1.	Altafrin	Phenylephrine	Look	The pair has sufficient orthographic differences
2.	Ofev***	Nintedanib	Look	The pair has sufficient orthographic differences
3.	Ofirmev	Acetaminophen	Look	The pair has sufficient orthographic differences
4.	Abraxane	Paclitaxel	Look	The pair has sufficient orthographic differences
5.	(b) (4)	(b) (4)	Look	The pair has sufficient orthographic differences
6.	Afaxin	Vitamin A plamitate	Look	Identified in previous review. Unable to find product characteristics in commonly used drug databases.
7.	Afrin Original, No Drip extra moisturizing, No drip original pump mist, No drip severe congestion, No drip sinus pump mist, Original pump mist, Severe congestion, sinus	Oxymetazoline	Look	The pair has sufficient orthographic differences
8.	Afrinol	Pseudoephedrine	Look	The pair has sufficient orthographic differences
9.	Alenaze D	Brompheniramine, phenylephrine	Look	The pair has sufficient orthographic differences
10.	Allegra	Fexofenadine	Look	The pair has sufficient orthographic differences
11.	Aplenzin	Bupropion HBr	Look	The pair has sufficient orthographic differences
12.	Atralin	Tretinoin	Look	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 Afrezza	Failure preventions
13.	Atripla	Efavirenz, emtricitabine, tenofovir disoproxil fumarate	Look	The pair has sufficient orthographic differences
14.	Atuss DS	Dextromethorphean, pseudoephedrine, chlorpheniramine	Look	The pair has sufficient orthographic differences
15.	Avinza	Morphine sulfate	Look	The pair has sufficient orthographic differences
16.	Cefizox	Ceftizoxime	Look	The pair has sufficient orthographic differences
17.	Strattera	atomoxetine	Sound	The pair has sufficient phonetic differences
18.	Alprazolam		Sound	The pair has sufficient phonetic differences
19.	Cyclessa	Ethinyl estradiol/desogestrel	Sound	The pair has sufficient phonetic differences
20.	Effexor	Venlafaxine	Look and Sound	The pair has sufficient orthographic and phonetic differences
21.	Afresa***	Insulin human [rDNA origin] Inhalation Powder	Look and Sound	Proposed name for this same product that was found unacceptable in a previous review (OSE RCM #2007-2449, dated June 20, 2009) because our evaluation determined that the name was vulnerable to confusion with the currently marketed product Apidra.
22.	Iressa	Gefitinib	Look and Sound	The pair has sufficient orthographic and phonetic differences
23.	(b) (4)	(b) (4)	Look and Sound	Proposed name for a generic product was not recommended in a previous review (OSE RCM #04-0094, dated May 19, 2004) because of the sponsor's proposal (b) (4) and concerns about the possibility of errors resulting from confusion from the proliferation of

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

				those suffixes. ANDA #076916 was approved on December 28, 2008 without a proprietary name
24.	Adrucil	Fluorouracil	Look and Sound	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.

No.	**Proposed name: Afrezza** **Dosage Form: powder for inhalation** **Strengths: 3 units & 6 units per cartridge** **Usual Dose: Inhale with meals (three times a day). Cartridge delivers 3 units or 6 units**	**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.	**Abreva** (Docusanol) - Topical Cream 10% (2g) - Apply 5 times/day to affected area of face or lips. Start at first sign of cold sore or fever blister and continue until healed	**Orthographic Similarities** - 'Afre' and 'Abre' may appear similar when scripted **Overlapping Product Characteristics** - Frequency of Administration (Both products can be administered multiple times a day)	**Orthographic Differences** - If the name Afrezza is scripted with the letter string 'zz' as a down stroke, it also helps decrease orthographic similarity between the names. Additionally, the corresponding letter strings '-zza' and '-va' appear different when scripted. **Differing Product Characteristics** - Units (units vs. "small amount")
2.	**Afluria** (Influenza Type A and B vaccine) - Inject 0.5 mL intramuscularly per dose according to prescribing information	**Orthographic Similarities** - Both names start with the letter string 'Af' - Both names contain 7 letters - Both names end in 'a'	**Orthographic Differences** - 'rezz' and 'luri' appear different when scripted due to two down strokes ('zz') **Differing Product Characteristics** - Strength (3 units and 6 units vs. 450 mcg/5 mL) - Usual Dose (Multiples of 3 units and 6 units vs. 0.5 mL) - Frequency of Administration (three times daily with meals vs. one time only)

No.	**Proposed name: Afrezza** **Dosage Form: powder for inhalation** **Strengths: 3 units & 6 units per cartridge** **Usual Dose: Inhale with meals (three times a day). Cartridge delivers 3 units or 6 units**	**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.	**Akurza** (Salicylic acid) - Topical cream: 6% (340 g) - Topical Solution: 6% (355 mL) - Apply to affected area once daily, preferably at bedtime and rinse off in the morning	**Orthographic Similarities** - 'Af' and 'Ak' may appear similar when scripted - Both names end in 'za' **Overlapping Product Characteristics** - Strength (6 units vs. 6%)	**Orthographic Differences** - 'rez' and 'ur' appear different when scripted **Differing Product Characteristics** - Dose (multiples of 3 units and 6 units vs. apply amount) - Frequency of Administration (three times daily with meals vs. once daily)
4.	**Albenza** (albedazole) - 200 mg oral tablets **Neurocysticercosis:** Oral: <60 kg: 15 mg/kg/day in 2 divided doses (maximum: 800 mg/day) for 8-30 days ≥60 kg: 800 mg/day in 2 divided doses for 8-30 days **Note:** Give concurrent anticonvulsant and steroid therapy during first week. **Hydatid:** Oral: <60	**Orthographic Similarities** - 'Af' and 'Al' may appear similar when scripted - Both names contain seven letters - Both names end in 'za' **Overlapping Product Characteristics** - Route of Administration (oral)	**Orthographic Differences** - Afrezza contains two upstrokes and two down strokes whereas Albenza contains three upstrokes. - Additionally, if the letter 'z' is scripted with a down stroke, then Afrezza also contains 2 additional down strokes whereas Albenza contains one down stroke. - 'rez' and 'ben' appear different when scripted **Differing Product Characteristics** - Strength (3 units, 6 units vs. 200 mg) - Dose (multiples of 3 units and 6 units vs. 2 tablets)

	kg: 15 mg/kg/day in 2 divided doses (maximum: 800 mg/day) ≥60 kg: 800 mg/day in 2 divided doses **Note:** Administer dose for three 28-day cycles with a 14-day drug-free interval in between. The manufacturer recommends a total of 3 cycles. ***Ancylostoma caninum***, ***Ascaris lumbricoides*** **(roundworm)**, ***Ancylostoma duodenale (hookworm)*****:** 400 mg as a single dose		
5.	(b) (4)		
6.	**Atarax** (hydroxyzine HCl) Tablet: 10 mg, 25 mg, 50 mg, 100 mg Syrup: 10 mg/5 mL 25 mg to 100 mg 3 to 4 times per daily Less than 6 years old: 50 mg divided dose	**Orthographic Similarities** - 'Af' and 'At' may appear similar when scripted **Overlapping Product Characteristics** - Route of Administration (oral) - Frequency of Administration (three times daily)	**Orthographic Differences** - 'rezza' and 'arax' appear different when scripted due to two downstrokes ('zz') **Differing Product Characteristics** - Strength (3 units, 6 units vs. 10 mg, 25 mg, 50 mg, 100 mg, 10 mg/5 mL) - Dose (multiples of 3 units and 6 units vs. 1 tablet, 5 mL) - Dosage Form (powder for inhalation vs. tablet, syrup)

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

No.	**Proposed name: Afrezza** **Dosage Form: powder for inhalation** **Strengths: 3 units & 6 units per cartridge** **Usual Dose: Inhale with meals (three times a day). Cartridge delivers 3 units or 6 units**	**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.	**Alesse 21, Alesse 28** (Levonorgestrel and Ethinyl Estradiol) Tablets: Days 1- 21: 0.1 mg and 0.02 mg 1 tablet once daily Note: Alesse 21 or Alesse 28 is no longer marketed. However, multiple generics that are available.	**Orthographic Similarities** - 'Af' and 'Al' may appear similar when scripted - 'zz' and 'ss' may appear similar when scripted **Overlapping Product Characteristics** - Route of Administration (oral)	**Orthographic Differences** - If 'zz' is scripted with down strokes 'rezza' and 'esse' appear different when scripted **Differing Product Characteristics** - Strength (3 units and 6 units vs. 0.1 mg/0.02 mg) - Dose (multiples of 3 units and 6 units vs. l tablet) - Frequency of Administration (three times daily with meals vs. once daily)
8.	**Apidra** (Insulin Glulisine) Solution for injection: 100 units/mL **Usual dose:** Subcutaneous: 0.5 to 1 unit/kg/day administered 15 minutes before a meal or within 20 minutes of starting a meal. The total daily insulin requirement may vary. Intravenous: 0.05 to 1 unit/mL infused IV in sodium chloride 0.9% using polyvinyl chloride (PVC) infusion bags	**Orthographic Similarities** - 'Af' and 'Ap' may appear similar when scripted - Letter strings 'za' and 'ra' may appear similar when scripted. **Overlapping Product Characteristics** - Dose and units (both are individualized insulin doses in units) - Frequency of Administration (three times daily)	**Orthographic Differences** - - 'frez' and 'pid' appear different when scripted. **Differing Product Characteristics** - Route of Administration (oral inhalation vs. sub-Q or intravenous injection)

No.	**Proposed name: Afrezza** **Dosage Form: powder for inhalation** **Strengths: 3 units & 6 units per cartridge** **Usual Dose: Inhale with meals (three times a day). Cartridge delivers 3 units or 6 units**	**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.	**Apriso** (Mesalamine) - 0.375 gm Extended release oral capsule Take 1.5 g (4 capsules) orally once daily in the morning. May be taken without regard to meals.	**Orthographic Similarities** - 'Afre' and 'Apri' may appear similar when scripted **Overlapping Product Characteristics** - Route of Administration (oral)	**Orthographic Differences** - 'zza' and 'so' appear different when scipted **Differing Product Characteristics** - Strength (3 units, 6 units vs. 0.375 mg) - Dose (multiples of 3 units and 6 units vs. 4 capsules) - Frequency of Administration (three times daily with meals vs. once daily)
10.	**Arzerra** (Ofatumumab) - 100 mg/5mL and 1000 mg/50 mL solution for injection Dose 1: 300 mg, followed by Dose 2-8: 2 g once weekly for 7 doses followed 4 weeks later by Dose 9-12: 2 g every 4 weeks for 4 doses Administered over 30 minute intravenous infusion **POCA: 51%**	**Orthographic Similarities** - Both names contain 7 letters and start with the letter 'A'. - 'rezza' and 'zerra' may look similar when the letter string 'zz' is scripted without a down stroke **Overlapping Product Characteristics** - Dose and Strength (Afrezza may be prescribed in terms of total dose. Thus, potential numerical overlap in dose is possible, especially if dangerous abbreviation 'u' is used and it may be misinterpreted for the number '0') For example, Arzerra 300 mg Afrezza 30 U	**Orthographic Differences** - Letters '-f-' and '-r-' appear different when scripted **Differing Product Characteristics** - Route of Administration Afrezza is administered via oral inhalation whereas Arzerra is administered via 30-minute intravenous infusion - Frequency of Administration (three times daily with each meal vs. on a weekly or monthly basis)

No.	**Proposed name: Afrezza** **Dosage Form: powder for inhalation** **Strengths: 3 units & 6 units per cartridge** **Usual Dose: Inhale with meals (three times a day). Cartridge delivers 3 units or 6 units**	**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.	**Oforta** (Fludarabine) - 10 mg oral tablets - 25 mg/m^2 to 40 mg/m^2 once daily on days 1 through 5 every 4 weeks.	**Orthographic Similarities** - 'Af-' and 'Of' may appear similar when scripted **Overlapping Product Characteristics** - Dose (Oforta's usual dose depends on the indication and person's BSA. Thus, Oforta's dose may be fluctuating. As a result, the overlap between Afrezza's strength or achievable dose and Oforta's strength and usual dose is possible) - Route of Administration (oral)	**Orthographic Differences** - 'rezza' and 'orta' appear different when scripted due to two down strokes ('zz') vs. on upstroke ('t') **Differing Product Characteristics** -Frequency of Administration (three times daily with meals vs. once daily for 5 days every 4 weeks)

No.	**Proposed name: Afrezza** **Dosage Form: powder for inhalation** **Strengths: 3 units & 6 units per cartridge** **Usual Dose: Inhale with meals (three times a day).** **Cartridge delivers 3 units or 6 units**	**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.	**Atreza** (Atropine Sulfate) - 0.4 mg oral tablets - 0.4 mg to 1.2 mg Every 4 to 6 hours Note: Identified in Redbook. Atreza is deactivated. **POCA ortho + phonetic: 86%** **Ortho: 80%** **Phonetic: 91%**	**Orthographic Similarities** - Both names start with letter 'A' and contain two upstrokes next to each other in the beginning of the names. Additionally, the letter strings 'Afre' and 'Atre' may appear similar when scripted. **Phonetic Similarities** - Both names begin with the letter 'A', and can share a similar phonetic ending '-suh'. Additionally the names can be pronounced similarly (a-fres-suh vs. a-tres-uh) **Overlapping Product Characteristics** - Dose (Afrezza's dose can be written as 4 units of subcutaneous insulin. Atreza's strength is 0.4 mg) - Frequency of Administration (Both products can be administered multiple times a day) - Route of Administration (oral)	**Orthographic Differences** The orthographic differences in the name, in addition to different product characteristics, minimize the likelihood of medication error in the usual practice setting. The name Afrezza contains 7 letters whereas the name Atreza contains 6 letters, which makes Afrezza appear longer due to additional wide letter 'z' in the name. **Differing Product Characteristics** - Dosing Units (Afrezza is dosed in terms of units whereas Atreza is dosed in terms of mg) Additionally, Atreza is discontinued brand of atropine tablets. Although most prescribers order atropine by established name rather than a brand name, even if prescribers specifies the Atreza product and omits the strength, the prescriber will be including the ordered dose in terms of number of tablets or other dose descriptor, which will help the differentiation Atreza between Afrezza.

No.	**Proposed name: Afrezza** **Dosage Form: powder for inhalation** **Strengths: 3 units & 6 units per cartridge** **Usual Dose: Inhale with meals (three times a day).** **Cartridge delivers 3 units or 6 units**	**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.	**Aflexa** (Glucosamine) - 500 mg ral capsules -1 capsule by mouth three times daily	**Orthographic similarities** - Both start with 'Af' - Both end with 'a' **Phonetic Similarities** - Both start with 'Af' - Both end with 'a' **Overlapping Product Characteristics** - Route of Administration (oral) - Frequency of Administration (three times daily)	**Orthographic Differences** - 'r' and 'l' appear different when scripted **Differing Product Characteristics** - Strength and Dose (multiples of 3 units and 6 units vs. 500 mg/1 capsule)

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

/s/

SARAH K VEE
01/13/2014

YELENA L MASLOV
01/13/2014

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

Date:	December 9, 2010
Application Type/Number:	NDA 022472
Through:	Zachary Oleszczuk, Pharm.D., Team Leader Denise Toyer, Pharm.D., Deputy Director Division of Medication Error Prevention and Analysis
From:	Yelena Maslov, Pharm.D., Safety Evaluator Division of Medication Error Prevention and Analysis
Subject:	Proprietary Name Review
Drug Name(s):	Afrezza (Insulin human [rDNA origin]) Inhalation Powder 10 unit and 20 unit cartridges
Applicant/sponsor:	MannKind Corporation
OSE RCM #:	2010-1578

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

CONTENTS

EXECUTIVE SUMMARY

This review summarizes DMEPA's proprietary name risk assessment of Afrezza (Insulin human [rDNA origin]) Inhalation Powder. Our evaluation did not identify concerns that would render the name unacceptable based on the product characteristics and safety profile known at the time of this review. Thus, DMEPA finds the proposed proprietary name, Afrezza, acceptable for this product (see Section 4 for full discussion).

DMEPA considers this a final review; however, if approval of the NDA is delayed beyond 90 days from the date of this review, the Division of Metabolism and Endocrinology Products should notify DMEPA because the proprietary name must be re-reviewed prior to the new approval date. Additionally, if any of the proposed product characteristics as stated in this review are altered, DMEPA rescinds this finding and the name must be resubmitted for review. The conclusions upon re-review are subject to change.

1 BACKGROUND

1.1 INTRODUCTION

This review responds to a request from MannKind Corporation, dated September 24, 2010, for a re-assessment of the proposed proprietary name, Afrezza, regarding the promotional nature and potential name confusion with other proprietary or established drug names in the usual practice setting.

1.2 REGULATORY HISTORY

Afrezza Inhalation Powder is a 505 (b)(1) application under NDA 022472 originally submitted to the FDA on March 16, 2009. DMEPA initially reviewed the name, Afrezza, and found it acceptable, based on the provided product characteristics, on December 8, 2009 in OSE Review #2009-1471. On March 12, 2010, The Application received a Complete Response.

The Applicant submitted a response to the Complete Response to the FDA on June 29, 2010. Additionally, the Applicant submitted a proprietary name request for Afrezza and (b) (4) (b) (4) for the product, which DMEPA found unacceptable. This assessment was communicated to the Applicant via telephone conference on August 24, 2010. The Applicant submitted a proprietary name withdrawal request for the name Afrezza and (b) (4) r on August 27, 2010.

1.3 PRODUCT INFORMATION

Afrezza Inhalation Powder is delivered via re-usable, breath-powered, high resistance, dry powder Gen2 inhaler. Insulin is intended for the treatment of adults with diabetes mellitus. Afrezza Inhalation Powder is proposed to be marketed in single dose cartridges of 10 units or 20 units. Each cartridge requires one inhalation to deliver the full dose. The 10 unit cartridge delivers approximately 4 units inhaled insulin and the 20 unit cartridge delivers approximately 8 units inhaled insulin to the patient. Patient specific factors affect the end amount of insulin delivered including health of patient (e.g., FEV1), concomitant health conditions, and user technique.

Insulin naïve patients should start on10 unit dose of Insulin (approximately 4 inhaled units) at each meal and titrate to the dose necessary to control blood glucose. For all other patients, the starting dose of Afrezza will be based on the total daily dose of subcutaneous insulin. Patients should replace 50% of the total daily insulin dose with a corresponding dose of Afrezza Inhalation Powder divided between main meals, while the remaining 50% of total dose of subcutaneous insulin will be given as basal long-acting subcutaneous insulin. The prandial dose of Afrezza should be adjusted based on blood glucose levels.

Afrezza Inhalation Powder should be stored in the refrigerator (2°C to 8°C) for up to 24 months. However, it can be stored at the temperature of 25°C with excursions between 15° to 30° C

permitted for 10 days. Once the blister strip is opened, all 3 cartridges inside of that strip should be used within 72 hours. Inhaler can be stored at the temperature of 25°C with permitted excursions between 15° to 30° C.

2 METHODS AND MATERIALS

Appendix A describes the general methods and materials used by the Division of Medication Error Prevention and Analysis (DMEPA) when conducting a proprietary name risk assessment for all proprietary names. Sections 2.1 and 2.2 identify specific information associated with the methodology for reviewing the proposed proprietary name, Afrezza.

2.1 SEARCH CRITERIA

For this review, particular consideration was given to drug names beginning with the letter 'A' when searching to identify potentially similar drug names, as 75% of the confused drug names reported by the USP-ISMP Medication Error Reporting Program involve pairs beginning with the same letter.[1,2]

To identify drug names that may look similar to Afrezza, DMEPA safety evaluators also consider the orthographic appearance of the name on lined and unlined orders. Specific attributes taken into consideration include the length of the name (seven letters), downstrokes (three, lower case letter 'f' and two letters 'z'), upstrokes (two, capital letter 'A' and lower case letter 'f'), cross-strokes (one, lower case letter 'f'), and dotted letters (none). Additionally, several letters in Afrezza may be vulnerable to ambiguity when scripted (See Appendix B) As such, DMEPA safety evaluators also considers these alternate appearances when identifying drug names that may look similar to Afrezza.

When searching to identify potential names that may sound similar to Afrezza, safety evaluators search for names with similar number of syllables (3), stresses (uh-FRESS-uh, AF-re-zah, Af-re-ZAH or Af-REE-za, etc.), and placement of vowel and consonant sounds. Additionally, the DMEPA staff considers that pronunciation of parts of the name can vary such as "Afrezza" may be interpreted as 'A-fresa' or 'Afre-zah'. The Applicant's intended pronunciation of the proprietary name, Afrezza, was taken into consideration (uh-FRESS-uh) as it was included in the external proprietary name assessment. However, because names are often mispronounced and/or spoken with regional accents and dialects, other potential pronunciations of the names are considered.

2.2 FDA PRESCRIPTION ANALYSIS STUDIES

In order to evaluate the potential for misinterpretation of the proposed proprietary name in handwriting and verbal communication of the name, the following inpatient and verbal orders were communicated during FDA prescription studies on August 3, 2010.

---

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

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

Figure 1: Afrezza study samples

Handwritten Requisition Medication Order	Verbal Prescription
Medication Order Afrezza inhale 4 units by mouth tid right before meal	Afrezza Inhaler Inhale 4 units by mouth three times a day right before a meal
Outpatient Prescription Afrezza 20 units #180 Inhale 16 units by mouth tid. right before meals	

3 RESULTS

3.1 DATA BASE AND INFORMATION SOURCES

DMEPA safety evaluator search yielded a total of eleven (n=11) names as having some similarity to the name, Afrezza.

Ten (n=10) of the eleven names were thought to look like Afrezza by the safety evaluators. These names are Afrinol, Afaxin, Oforta, Atuss DS/Atuss HS, Abreva, Abraxane, Aplenzin, Allegra, Afrin/Afrin Sinus, and Afluria.

The remaining one name (n=1), Afreeza, was though to look and sound like Afrezza by the safety evaluators.

Additionally, DMEPA did not identify any United States Adopted Names (USAN) stems in the proposed proprietary name as of October 7, 2010.

3.2 EXPERT PANEL DISCUSSION

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

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

3.3 FDA PRESCRIPTION ANALYSIS STUDIES

A total of 31 practitioners responded to the prescription analysis studies. None of the responses overlapped with other drug names. Fifteen respondents (n=15) interpreted the proposed proprietary name correctly as 'Afrezza', with fourteen correct interpretation occurring with outpatient orders (n=14) and one correct interpretation occurring in the inpatient setting (n=1). The most common misinterpretation of the remaining 17 prescriptions occurred with misinterpreting the letter string '-zz-' as '-ve-' (n=6) and '-re-' (n=4). See Appendix C for the complete listing of interpretations from the verbal and written prescription studies.

3.4 COMMENTS FROM THE DIVISION OF METABOLISM AND ENDOCRINOLOGY PRODUCTS (DMEP)

3.4.1 Initial Phase of Review

The Division of Metabolism and Endocrinology Products (DMEP) did not communicate any comments regarding the proprietary name, Afrezza to DMEPA during DMEPA's current assessment of this proprietary name.

3.4.2 Midpoint of Review

DMEPA notified DMEP via email on October 22, 2010 that we do not object to the use of the proprietary name, Afrezza. Per email correspondence on October 28, 2010 DMEP indicated that they concur with DMEPA's recommendations.

3.4 SAFETY EVALUATOR RISK ASSESSMENT OF THE PROPOSED PROPRIETARY NAME

The primary safety evaluator identified twenty-two names (n=22), which were thought to look or sound familiar to Afrezza and represent a potential source of drug confusion.

Twelve names (n=12) of the 22 were thought to look like Afrezza. These names are Arzerra, Alenaze D, (b) (4) Atralin, Alesse 21/Alesse 28, Afrazine, Akurza, Cefizox, Albenza, Atripla, Avinza, and Apidra.

Four names (n=4) were thought to sound like Afrezza by the primary safety evaluator. These names are Iressa, Cyclessa, Straterra, and Apriso.

The remaining six names (n=5) were thought to look alike and sound alike. These names are Afresa***, (b) (4) Aflexa, Atreza, and Adrucil.

Thus, a total of thirty-two (n=32) names were evaluated for the potential similarity to the proposed name, Afrezza.

4 DISCUSSION

4.1 PROMOTIONAL ASSESSMENT

DDMAC did not find the name Afrezza promotional on July 29, 2010. DMEPA and DMEP concurred this finding.

4.2 SAFETY ASSESSMENT

In total, DMEPA evaluated thirty-two names (n=32). Eleven (n=11) of the 32 names were eliminated from the further analysis for the following reasons: six names (n=6) lacked orthographic and/or phonetic similarity, one name (n=1) was withdrawn from the US market, two names (n=2) were found unacceptable by DMEPA and have never been marketed, one name (n=1) is a name of the product that is marketed in a foreign county (See Appendices D through G).

Additionally, attempts by the primary safety evaluator to identify a drug product associated with the name Afreeza determined that this name was misspelled in one of the search databases used for name evaluation (Dogpile, i.e. Afreeza for Afrezza). Therefore, the name Afreeza has been removed from further analysis.

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

Failure Mode and Effect Analysis (FMEA) was then applied to determine if the proposed proprietary name could potentially be confused with the remaining twenty-one names (n=21) and, thereby, lead to medication errors. This analysis determined that the name similarity between Afrezza and all 21 remaining products was unlikely to result in medication errors for the reasons presented in Appendices H through K.

5 CONCLUSIONS AND RECOMMENDATIONS

Our assessment of the proprietary name indicates that the proposed name, Afrezza, is not vulnerable to name confusion that could lead to medication errors, nor is the name considered promotional. Thus, DMEPA has no objection to the proposed name, Afrezza, for this product at this time. The Applicant will be notified via letter.

Additionally, if any of the proposed product characteristics as stated in this review are altered, DMEPA rescinds this finding and the name must be resubmitted for review. The conclusions upon re-review are subject to change.

If you have further questions or need clarifications, please contact Margarita Tossa, project manager, at 301-796-4053.

5.1 COMMENTS TO THE APPLICANT

We have completed our re-review of the proposed proprietary name, Afrezza, and we have concluded that it is acceptable.

DMEPA considers this a final review; however, if approval of the NDA is delayed beyond 90 days from the date of this review, the proposed proprietary name must be re-reviewed 90 days before approval of the NDA. If any of the proposed product characteristics as stated in this review are altered, DMEPA rescinds this finding and the name must be resubmitted for review. The conclusions upon re-review are subject to change.

6 REFERENCES

1. Previous OSE Review

Pincock, Laura. OSE Review #2009-1471, Afrezza (Insulin Inhalation Powder) Proprietary Name Review.

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

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

3. 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.

4. 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.

5. The Document Archiving, Reporting, and Regulatory Tracking System (DARRTS)

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

6. 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.

7. 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.

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

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

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

USPTO provides information regarding patent and trademarks.

10. 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.

11. 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.

12. 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.

13. Stat!Ref (www.statref.com)

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

14. USAN Stems (http://www.ama-assn.org/ama/pub/category/4782.htmL)

USAN Stems List contains all the recognized USAN stems.

15. Red Book Pharmacy's Fundamental Reference

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

16. Lexi-Comp (www.lexi.com)

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

17. Medical Abbreviations Book

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

APPENDICES

Appendix A:

FDA's Proprietary Name Risk Assessment considers the potential for confusion between the proposed proprietary name and the proprietary and established names of drug products existing in the marketplace and those pending IND, NDA, BLA, and ANDA products currently under review by the Center. DMEPA defines a medication error as any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer. [3]

For the proposed proprietary name, DMEPA staff search a standard set of databases and information sources to identify names with orthographic and phonetic similarity and hold a Center for Drug Evaluation and Research (CDER) Expert Panel discussion to gather professional opinions on the safety of the proposed proprietary name. DMEPA staff also conducts internal CDER prescription analysis studies. When provided, DMEPA considers external prescription analysis study results and incorporate into the overall risk assessment.

The Safety Evaluator assigned to the Proprietary Name Risk Assessment is responsible for considering the collective findings, and provides an overall risk assessment of the proposed proprietary name. DMEPA bases the overall risk assessment on the findings of a Failure Mode and Effects Analysis (FMEA) of the proprietary name, and focuses on the avoidance of medication errors.

FMEA is a systematic tool for evaluating a process and identifying where and how it might fail. [4] DMEPA uses FMEA to analyze whether the drug names identified with orthographic or phonetic similarity to the proposed proprietary name could cause confusion that subsequently leads to medication errors in the clinical setting. DMEPA uses the clinical expertise of its staff to anticipate the conditions of the clinical setting where the product is likely to be used based on the characteristics of the proposed product.

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

---

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

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

Typical product characteristics considered when identifying drug names that could potentially be confused with the proposed proprietary name include, but are not limited to; established name of the proposed product, proposed indication of use, dosage form, route of administration, strength, unit of measure, dosage units, recommended dose, typical quantity or volume, frequency of administration, product packaging, storage conditions, patient population, and prescriber population. Because drug name confusion can occur at any point in the medication use process, DMEPA staff considers the potential for confusion throughout the entire U.S. medication use process, including drug procurement, prescribing and ordering, dispensing, administration, and monitoring the impact of the medication.[5] DMEPA provides the product characteristics considered for this review in section one.

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

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

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

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

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

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

1. Database and Information Sources

DMEPA staff conducts searches of the internet, several standard published drug product reference texts, and FDA databases to identify existing and proposed drug names that may sound-alike or look-alike to the proposed proprietary name using the criteria outlined in Section 2.1. Section 6 provides a standard description of the databases used in the searches. To complement the process, the DMEPA staff use a computerized method of identifying phonetic and orthographic similarity between medication names. The program, Phonetic and Orthographic Computer Analysis (POCA), uses complex algorithms to select a list of names from a database that have some similarity (phonetic, orthographic, or both) to the trademark being evaluated. Lastly, the DMEPA staff review the USAN stem list to determine if any USAN stems are present within the proprietary name. The individual findings of multiple safety evaluators are pooled and presented to the CDER Expert Panel.

2. CDER Expert Panel Discussion

DMEPA conducts an Expert Panel Discussion to gather CDER professional opinions on the safety of the proposed product and the proposed proprietary name. The Expert Panel is composed of Division of Medication Errors Prevention (DMEPA) staff and representatives from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The Expert Panel also discusses potential concerns regarding drug marketing and promotion related to the proposed names.

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

3. FDA Prescription Analysis Studies

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

In order to evaluate the potential for misinterpretation of the proposed proprietary name in handwriting and verbal communication of the name, inpatient medication orders and/or outpatient prescriptions are written, each consisting of a combination of marketed and unapproved drug products, including the proposed name. These orders are optically scanned and one prescription is delivered to a random sample of the 123 participating health professionals via e-mail. In addition, a verbal prescription is recorded on voice mail. The voice mail messages are then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants send their interpretations of the orders via e-mail to DMEPA.

4. Comments from the OND review Division or Generic drugs

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

The OND or OGD Regulatory Division is contacted a second time following our analysis of the proposed proprietary name. At this point, DMEPA conveys their decision to accept or reject the name. The OND or OGD Regulatory Division is requested to concur/not concur with DMEPA's final decision.

5. Safety Evaluator Risk Assessment of the Proposed Proprietary Name

The primary Safety Evaluator applies his/her individual expertise gained from evaluating medication errors reported to FDA, conducts a Failure Mode and Effects Analysis, and provides an overall risk assessment of name confusion. Failure Mode and Effects Analysis (FMEA) is a systematic tool for evaluating a process and identifying where and how it might fail.[6] When applying FMEA to assess the risk of a proposed proprietary name, DMEPA seeks to evaluate the potential for a proposed proprietary name to be confused with another drug name because of name confusion and, thereby, cause errors to occur in the medication use system. FMEA capitalizes on the predictable and preventable nature of medication errors associated with drug name confusion. FMEA allows the Agency to identify the potential for medication errors due to orthographically or phonetically similar drug names prior to approval, where actions to overcome these issues are easier and more effective than remedies available in the post-approval phase.

In order to perform an FMEA of the proposed name, the primary Safety Evaluator must analyze the use of the product at all points in the medication use system. Because the proposed product is has not been marketed, the primary Safety Evaluator anticipates the use of the product in the usual practice settings by considering the clinical and product characteristics listed in Section one. The Safety Evaluator then analyzes the proposed proprietary name in the context of the usual

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

practice setting and works to identify potential failure modes and the effects associated with the failure modes.

In the initial stage of the Risk Assessment, the Safety Evaluator compares the proposed proprietary name to all of the names gathered from the above searches, Expert Panel Discussion, and prescription studies, external studies, and identifies potential failure modes by asking:

> ***"Is the proposed proprietary name convincingly similar to another drug name, which may cause practitioners to become confused at any point in the usual practice setting?"***

An affirmative answer indicates a failure mode and represents a potential for the proposed proprietary name to be confused with another proprietary or established drug name because of look- or sound-alike similarity. If the answer to the question is no, the Safety Evaluator is not convinced that the names posses similarity that would cause confusion at any point in the medication use system, thus the name is eliminated from further review.

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

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

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

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

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

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

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

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

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

If DMEPA objects to a proposed proprietary name on the basis that drug name confusion could lead to medication errors, the primary Safety Evaluator uses the FMEA process to identify strategies to reduce the risk of medication errors. DMEPA is likely to recommend that the Sponsor select an alternative proprietary name and submit the alternate name to the Agency for DMEPA to review. However, in rare instances FMEA may identify plausible strategies that

could reduce the risk of medication error of the currently proposed name. In that instance, DMEPA may be able to provide the 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 Sponsor. However, the safety concerns set forth in criteria a through e are supported either by FDA regulation or by external healthcare authorities, including the Institute of Medicine (IOM), World Health Organization (WHO), the Joint Commission, and the Institute for Safe Medication Practices (ISMP). These organizations have examined medication errors resulting from look- or sound-alike drug names and called for regulatory authorities to address the issue prior to approval. Additionally, DMEPA contends that the threshold set for the Proprietary Name Risk Assessment is reasonable because proprietary drug name confusion is a predictable and a preventable source of medication error that, in many instances, the Agency and/or 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. . (See Section 4 for limitations of the process).

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

<u>Appendix B:</u> Letters with possible orthographic or phonetic misinterpretation

Letters in Name, Afrezza	Scripted may appear as	Spoken may be interpreted as
Capital 'A'	'ce', 'FL', 'H', 's'	Any vowel
Lower case 'a'	'el', 'd', 'o'	Any vowel
Lower case 'f'	't', 'd', 'l'	'v', 'p'
Letter string 'r'	'c', 'e', 'n', 's', 't', 'x', 'z'	
Lower case 'e'	'a', 'c', 'i', 'l', or 'p'	Any vowel
Lower case 'z'	'c', 'e', 'g', 'n', 'm' 'q', 'r', 's', 'v'	'c', 's', 'x'

<u>Appendix C:</u> FDA Prescription study for Afrezza from 08/03/2010

<u>Figure 1:</u> Afrezza study samples

Handwritten Requisition Medication Order	Verbal Prescription
<u>Medication Order</u> Afrezza inhale 4 units by mouth tid right before meal	Afrezza Inhaler Inhale 4 units by mouth three times a day right before a meal
<u>Outpatient Prescription</u> Afrezza 20 units #180 Inhale 16 units by mouth tid. right before meals	

Table 1: Responses to prescription study

Inpatient Medication Order 08/03/2010	Outpatient Prescription Order 08/03/2010	Voice Prescription 08/03/2010
Afrevea	Afrezza	Aprisa
Afnerra	Afrezza	Afrisa
Afrevea	Afrezza	Ofpriza
Afrevea	Afrezza	Abriza
Afrevea	Afrezza	
Afrevea	Afrezza	
Afnervea	Afrezza	
Afrerea	Afrezza	
Afreva	Afrezza	
Afrerea	Afrezza	
Alnerra	Afrezza	
Afnerea	Afrezza	
Afrerea	Afrezza	
Afrezza	Afrezza	

Appendix D: Names of products that lack convincing orthographic and/or phonetic similarity

Drug Product Name	Drug Product Name
Afrinol	Allegra
(b) (4)	Abraxane
Alenaze D	Strattera

Appendix E: Name of the products withdrawn from the United States market

Proprietary Name	Similarity to Afrezza	Status
Afaxin (Vitamin A Palmitate) Capsules 50,000 Units Base	Look alike	Discontinued

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

Appendix F: Name of the product that have not been approved

Proprietary Name	Similarity to Afrezza	Status of a Product Name
Afresa***	Look alike and sounds alike	Proposed name for this same product that was found unacceptable in a previous review (OSE RCM #2007-2449, dated June 20, 2009) because our evaluation determined that the name was vulnerable to confusion with the currently marketed product Apidra. Therefore, the name Afresa*** is no lonfer under consideration for use as a proprietary name of the drug product.
(b) (4) *** (Desogestrel and Ethinyl Estradiol)	Looks alike and sounds alike	Proposed name for a generic product was not recommended in a previous review (OSE RCM #04-0094, dated May 19, 2004) because of the sponsor's proposal (b) (4) and concerns about the possibility of errors resulting from confusion from the proliferation of those suffixes. ANDA #076916 was approved on December 28, 2008 without a proprietary name

Appendix G: Products marketed in the foreign country

Proprietary Name	Similarity to Afrezza	Country of the marketed product
Afrazine (Oxymetazoline)	Look alike	United Kingdom and Ireland

Appendix H: **Names of the products with no overlap in dose and/or strength**

Product name with potential for confusion	**Similarity to Afrezza**	**Dosage Form and Strength**	**Usual Dose (If applicable)**
Afrezza (Insulin Human rDNA Inhalation Powder)	**N/A**	**Strength: 10 units and 20 units, which equals to 4 units or 8 units of subcutaneous insulin respectively. Thus, maybe labeled as strength, dose, or both**	**Inhale orally using the (b) (4) Inhaler with meals (three times a day). Cartridge delivers 4 units (10 unit strength) or 8 units (20 unit strength)**
Akurza (Salicylic acid)	Look alike	Topical cream: 6% (340 g) Topical Solution: 6% (355 mL)	Apply to affected area once daily, preferably at bedtime and rinse off in the morning
Afrin/Afrin Sinus (Oxymetazoline)	Look alike	Nasal Solution: 0.05%	Apply or spray nasally up to every 12 hours for 3 days
Aplenzin (Bupropion)	Look alike	Extended Release Tablets: 174 mg, 348 mg, 522 mg	Start at 174 mg tablet orally once daily in the morning. Increase, if needed, as tolerated to maximum of 522 mg once daily in the morning
Atralin (Tretinoin)	Look alike	Topical gel: 0.05%	Apply to affected area once daily at bedtime
Cefizox (Ceftizoxime)	Look alike	Injection: 1 g/50 mL (20 mg/mL) and 2 g/50 mL (40 mg/mL) Powder for Injection: 500 mg, 1 g, and 2 g	500 mg, 1 g, or 2 g via intramuscular injection or intravenous infusion over 30 minutes every 8 to 12 hours depending on the organism susceptibility and severity of infection. Life-threatening infections require 3 to 4 g every 8 hours.

Appendix I: Single Strength Products with Differentiating Product Characteristics

Product name with potential for confusion	**Similarity to Afrezza**	**Dosage form/ Strength**	**Usual Dose**	**Other Differentiating Product Characteristics**
Afrezza (Insulin Human rDNA Inhalation Powder)	**N/A**	**Strength: 10 units and 20 units, which equals to 4 units or 8 units of subcutaneous insulin respectively. Thus, maybe labeled as strength, dose, or both**	**Inhale orally using the (b) (4) Inhaler with meals (three times a day). Cartridge delivers 4 units (10 unit strength) or 8 units (20 unit strength)**	**N/A**
Alesse 21 (Levonorgestrel and Ethinyl Estradiol) Alesse 28 (Levonorgestrel and Ethinyl Estradiol) Note: Alesse 21 or Alesse 28 is no longer marketed. However, multiple generics that are available.	Looks alike	Tablets: Days 1- 21: 0.1 mg and 0.02 mg Tablets: Days 1- 21: 0.1 mg and 0.02 mg Days 21-28: 7 inert tablets	Take 1 tablet daily	Dosage Form Inhalation powder vs. tablet Strength 10 units and 20 units vs. 0.1 mg/0.02 mg Usual Dose 4 units and 8 units vs. l tablet Frequency of Administration Three times a day (with each meal) vs. one time only
Afluria (Influenza A and Influenza B) 2010-2011	Look alike	Injection: 450 mcg/5 mL (90 mcg/mL)	0.5 mL (45 mcg) via intramuscular injection as a single dose	Dosage Form Inhalation powder vs. Injection Strength 10 units and 20 units vs. 450 mcg/5 mL Usual Dose 4 units and 8 units vs. 0.5 mL Route of Administration Oral inhalation vs. intramuscular Frequency of Administration Three times a day (with each meal) vs. one time only

Cyclessa (Desogestrel and Ethinyl Estradiol)	Sound alike	Tablets: Day 1-7:0.125 mg and 0.025 mg; Day 8-14: 0.15 mg and 0.025 mg; Day 14-21: 0.1 mg and 0.025 mg Day 21-28: 7 green inactive tablets (28s)	Take one tablet daily	Dosage Form Inhalation powder vs. tablet Strength 10 units and 20 units vs. 0.125 mg and 0.025 mg; then 0.15 mg and 0.025 mg; then 0.1 mg and 0.025 mg (7 tablets of each strength); Usual Dose 4 units and 8 units vs. l tablet Frequency of Administration Three times a day (with each meal) vs. one time only
Iressa (Geftinib)	Sound alike	Tablet: 250 mg	250 mg/day; consider 500 mg/day in patients receiving effective CYP3A4 inducers (e.g., rifampin, phenytoin)	Dosage Form Inhalation powder vs. tablet Strength 10 units and 20 units vs. 250 mg Usual Dose 4 units and 8 units vs. 250 mg to 500 mg Frequency of Administration Three times a day (with each meal) vs. once daily
Aflexa (Glucosamine) Non-prescription dietary supplement	Look alike and sound alike	Tablets: 340 mg	1.5 g/ day as a single dose or in divided doses	Dosage Form Inhalation powder vs. tablet Strength 10 units and 20 units vs. 340 mg Usual Dose 4 units and 8 units vs. 1.5 g/day

<u>Appendix K:</u> Potentially confusing names with overlap in strength, but analysis indicates low potential for confusion

Failure Mode: Name Confusion	Causes (can be multiple)	Rationale for Failure Mode Prevention
Afrezza (Insulin Human rDNA Inhalation Powder) **Strength: 10 units and 20 units, which equals to 4 units or 8 units of subcutaneous insulin respectively. Thus, maybe labeled as strength, dose, or both**	**N/A**	**Inhale orally using the** (b) (4) **Inhaler with meals (three times a day). Cartridge delivers 4 units (10 unit strength) or 8 units (20 unit strength)**
Albenza (albedazole) Tablets 200 mg **Neurocysticercosis:** Oral: <60 kg: 15 mg/kg/day in 2 divided doses (maximum: 800 mg/day) for 8-30 days ≥60 kg: 800 mg/day in 2 divided doses for 8-30 days **Note:** Give concurrent anticonvulsant and steroid therapy during first week. **Hydatid:** Oral: <60 kg: 15 mg/kg/day in 2 divided doses (maximum: 800 mg/day) ≥60 kg: 800 mg/day in 2 divided doses **Note:** Administer dose for three 28-day cycles with a 14-day drug-free interval in between. The manufacturer recommends a total of 3 cycles. ***Ancylostoma caninum***, ***Ascaris lumbricoides*** **(roundworm)**, ***Ancylostoma duodenale (hookworm*:** Oral: 400 mg as a single dose	<u>Orthographic</u> Both names contain seven letters start with the letter A, and share the same suffix '-za'. Additionally, the letter strings 'Af-' and the corresponding letter string 'Al-' may be scripted to look similar <u>Route of Administration</u> Both products should be administered orally <u>Numerical Similarity in Strengths and Doses</u> It is possible for both products to have an overlap in numerical strengths and doses (e.g. Afrezza 20 units and Albenza 200 mg)	<u>Orthographic</u> Afrezza contains two upstrokes and two down strokes whereas Albenza contains three upstrokes. Additionally, if the letter 'z' is scripted with a down stroke, then Afrezza also contains 2 additional down strokes whereas Albenza contains one down stroke. Also, the letter string '-rez-' does not appear similar when scripted to the corresponding letter string '-ben-' <u>Dosing</u> Although 20 vs. 200 mg may look similar to each other, a practitioner would have to use a trailing zero to express the strength or dose of Afrezza. Usual practice would not typically use trailing zeros. Thus, this risk would be minimized.

Atripla (Efavirenz/Emtricitabine/Tenofovir) Tablets Strength 600 mg/200 mg/300 mg Usual Dose 1 tablet Route of Administration Orally Frequency of Administration Once daily at bedtime	Orthographic similarity Both names contain 7 letters, two upstrokes positioned next to each other in the beginning of the names (‘Af-’ and ‘At-’), and start with the letter ‘A’. Additionally, the letter corresponding letter strings ‘Af-’ in Afrezza and ‘At-’ in Atripla may look similar when scripted.	The orthographic differences in the name, in addition to different product characteristics, minimize the likelihood of medication error in the usual practice setting. Orthographic Although both names contain two upstrokes positioned next to each other in the beginning of the names, the name Atripla contains one down stroke and one upstroke at the end of the name, whereas Afrezza may contain no down strokes or two down strokes next to each other, depending on the way the letter string ‘-zz-’ is scripted. Additionally, the corresponding letter strings ‘-zza’ in Afrezza and ‘-pla’ in Atripla lack orthographic similarity. Dosing Units 1 tablet vs. X units Frequency of Administration Afrezza should be administered at least three times a day (with each meal) whereas Atripla should be administered once daily at bedtime.
Apriso (Mesalamine) Delayed Release Capsules 0.375 g Usual Dose Take 1.5 g (4 capsules) orally once daily in the morning	Orthographic Both names start with the letter ‘A’ and the letter string ‘Afre-’ may be scripted to appear similar to the letter string ‘Apri-‘. Numerical Overlap in Dose 4 units vs. 4 capsules	Orthographic Apriso contains 1 downstroke in the beginning of the name whereas Afrezza contains 1 upstroke and 2 downstrokes at the end of the name. Additionally, the letter string ‘-zza’ does not appear similar when scripted to the letter string ‘-so’. Dosage Form Afrezza will be available as Inhalation Powder vs. Apriso is available in capsule Strength 10 units and 20 units vs. 0.375 mg Frequency of Administration Afrezza will be administered three times daily (with each meal) whereas Apriso is administered once daily

Adrucil (Fluorouracil) Injection Strength 500 mg/10 mL; 2.5 g/50 mL; and 5 g/100 mL (50 mg/mL) Usual Dose and Frequency Bolus Range: 300 mg/m^2 to 500 mg/m^2 once daily for 4 to 5 days every 28 days, or 600 mg/m^2 to 1500 mg/m^2 once weekly or every other week Continuous Infusion: 300 mg/m^2 to 1000 mg/m^2 daily for 4 to 5 days every 4 weeks, or 300 mg/m^2 indefinitely. Route of Administration Intravenously Note: Adrucil brand is no longer marketed. However, the generic Fluorouracil Injections are available.	Orthographic Both names contain 7 letters, two upstrokes next to each other in the beginning of the names, and start with letter 'A'. Additionally, the corresponding letter strings 'Afr-' and 'Adr-' may appear similar when scripted. Overlapping Numerical Similarity Afrezza's achievable dose may overlap with Adrucil's strength. For example: Afrezza 50 units Adrucil 50 mg/mL	The orthographic differences in the name, in addition to different product characteristics, minimize the likelihood of medication error in the usual practice setting. Orthographic Adricil contains a third upstroke at the end of the name, whereas Afrezza may contain two down strokes next to each other, if the letter string 'zz' is scripted as down stroke. Additionally, the corresponding letter strings '-ezza' and 'ucil' lack orthographic similarity when scripted. Dosage Form Afrezza is a powder for inhalation whereas Adrucil is an injection Dosing Units Afrezza is dosed in terms of units whereas Adrucil is dosed in terms of mg. Route of Administration Afrezza is administered via oral inhalation whereas Adrucil is administered via intravenous injection or infusion Frequency of Administration Afrezza is administered at least three times a day (with each meal) whereas Adricul is administered on a weekly or monthly basis.

Abreva (Docusanol) Topical Cream <u>Strength</u> 10% (2g) <u>Usual Dose</u> Apply 5 times/day to affected area of face or lips. Start at first sign of cold sore or fever blister and continue until healed <u>Route of Administration</u> Topically <u>Frequency of Administration</u> 5 times per day	<u>Orthographic similarity</u> Both names start with the latter 'A' and contain two upstrokes positioned next to each other in the beginning of the names ('Af-' and 'Ab.-'). Additionally, both products share the letter string '-re-' and the letter corresponding letter strings 'Af-' in Afrezza and 'Ab-' in Abreva may look similar when scripted. <u>Numerical Overlap in Strength</u> Afrezza's may be prescribed as 10 units. Abreva's strength is 10%. <u>Frequency of Administration</u> Both products can be administered multiple times a day	The orthographic differences in the name, in addition to different product characteristics, minimize the likelihood of medication error in the usual practice setting. <u>Orthographic</u> Afrezza contains 7 letters whereas Abreva contains 6 letters, thus making the name Afrezza appear longer due to wide letter 'z'. If the name Afrezza is scripted with the letter string 'zz' as a down stroke, it also helps decrease orthographic similarity between the names. Additionally, the corresponding letter strings '-zza' and '-va' lack orthographic similarity when scripted. <u>Dosing Units</u> Afrezza is dosed in terms of units whereas Abreva is dosed in terms of "small amount" <u>Dosage Form</u> Afrezza is a powder for inhalation whereas Abreva is a topical cream <u>Route of Administration</u> Afrezza is administered via oral inhalation whereas Abreva is applied topically.

Arzerra (Ofatumumab) Injection Strength 100 mg/5mL (20 mg/mL) Usual Dose Dose 1: 300 mg, followed by Dose 2-8: 2 g once weekly for 7 doses followed 4 weeks later by Dose 9-12: 2 g every 4 weeks for 4 doses Route of Administration Administered over 30-minute intravenous infusion	Orthographic Both names contain 7 letters and start with the letter 'A'. The corresponding letter strings '-rezza' in Afrezza and 'zerra' in Arzerra may look similar when the letter string 'zz' is scripted without a down stroke. Frequency of Administration If products are administered in a inpatient setting, it is possible for the products to be prescribed as a single dose. Numerical Overlap in Dose and Strength Practitioners may prescribe Afrezza in terms of total dose of inhaled insulin they would like a patient to inhale (e.g., Afrezza 30 units). Thus, potential numerical overlap in dose is possible, especially if practitioners use the dangerous abbreviation 'u' that may be misinterpreted for the number '0'. For example, Arzerra 300 Afrezza 30 U	The orthographic differences in the name, in addition to different product characteristics, minimize the likelihood of medication error in the usual practice setting. Orthographic Afrezza may contain two down strokes next to each other at the end of the name, if the letter string 'zz' is scripted as down strokes whereas Arezerra does not. Additionally, the corresponding letters '-f-' and '-r-' lack orthographic similarity when scripted. Dosage Form Afrezza is a powder for inhalation whereas Arzerra is an injection Route of Administration Afrezza is administered via oral inhalation whereas Arzerra is administered via 30-minute intravenous infusion Frequency of Administration Afrezza is administered at least three times a day (with each meal) whereas Arzerra is administered on a weekly or monthly basis.

Atuss DS (Chlorpheniramine Maleate, Dextromethorphan HBr, Pseudoephedrine HCl) Suspension Strength 4 mg/30 mg/30 mg per 5 mL Usual Dose 2.5 mL to 10 mL up to four times a day (½ teaspoonful to 2 teaspoonfuls) Route of Administration Orally Frequency of Administration Four times a day	Orthographic If the modifier 'DS' is dropped: Both names start with the letter 'A' and contain two upstrokes next to each other in the beginning of the name ('Af-'and 'At-'). Additionally, the corresponding letter string 'Afrezz' and the name Atuss may look similar when scripted. Frequency of Administration Both products can be administered multiple times a day	The orthographic differences in the name, in addition to different product characteristics, minimize the likelihood of medication error in the usual practice setting. Orthographic Afrezza contains 7 letters whereas Atuss contains 5 letters, making the name Afrezza appear longer. Additionally, if the letter string 'zz' in the name Afrezza is scripted as down stroke, then the corresponding letter string 'ss' would lack orthographic similarity when scripted. Also the use of the modifier 'DS' with the root name Atuss provides further differentiation between the two names. Dosing Units Afrezza is dosed in terms of units whereas Atuss DS is dosed in terms of mL Dosage Form Afrezza is powder for inhalation whereas Atuss is a suspension
Avinza (Morphine Sulfate) Extended-Release Tablets Strength 30 mg, 45 mg, 60 mg, 75 mg, 90 mg, 120 mg Usual Dose Start at 30 mg and titrate upward, if needed, as tolerated Route of Administration Orally Frequency of Administration Once daily	Orthographic Both names start with the letter 'A' and end with letter string '-za'. The corresponding letter strings 'Af-' and 'Av-' may look similar when scripted. Numerical Overlap in Dose and Strength Afrezza may be prescribed in terms of total dose to be inhaled, such as Afrezza 30 units or Afrezza 60 units. Thus, numerical overlap with Avinza's strengths is possible.	The orthographic differences in the name, in addition to different product characteristics, minimize the likelihood of medication error in the usual practice setting. Orthographic Afrezza contains two upstrokes next to each other in the beginning of the name whereas Avinza contains one upstroke. Additionally, Afrezza contains 2 down strokes and Avinza contains 1 down stroke. Dosing Units Afrezza is dosed in terms of units whereas Avinza is dosed in terms of mg. Frequency of Administration Afrezza should be administered at least three times a day (with each meal) whereas Avinza should be administered once daily

Apidra Apidra SoloStar (Insulin Glulisine) <u>Strength</u> Apidra: 100 units/mL (10 mL) Apidra SoloStar: 100 units/mL (15 mL) <u>Usual Dose</u> 0.2 units to 0.6 units/kg/day in three divided doses <u>Route of Administration</u> Subcutaneous Injection <u>Frequency of Administration</u> Usually three times a day	Orthographic Both names start with the letter 'A.' The corresponding letter strings '-za' in Afrezza and '-ra' in Apidra may appear similar when scripted. <u>Numerical Overlap in Strength</u> There is a numeric overlap between Afrezza's strength of 10 units and Apidra's strength of 100 units/mL (10 mL) <u>Numerical Overlap in Dose</u> Afrezza may be prescribed in terms of strength or total intended dose. Thus, these numerical values may overlap with Apidra's doses (10 units vs. 10 units) <u>Dosing Units</u> Both products are measured in units <u>Frequency of Administration</u> Both products are administered three times a day	The orthographic differences in the name, in addition to different product characteristics, minimize the likelihood of medication error in the usual practice setting. <u>Orthographic</u> Afrezza contains 2 upstrokes next to each other in the beginning of the name ('Af'), whereas Apidra contains 2 upstrokes in different positions of the name ('A' and 'd') and one down stroke ('p'). Additionally, the corresponding letter strings '-frez-' and '-pid-' lack orthographic similarity when scripted. <u>Route of Administration</u> Afrezza is administered via oral inhalation whereas Apidra is administered via subcutaneous injection.

Atreza (Atropine Sulfate) Tablets <u>Strength</u> 0.4 mg <u>Usual Dose</u> 0.3 mg to 1.2 mg <u>Route of Administration</u> Orally <u>Frequency of Administration</u> Every 4 to 6 hours Note: Atreza brand is no longer marketed. However, multiple generics are available.	<u>Orthographic</u> Both names start with letter 'A' and contain two upstrokes next to each other in the beginning of the names. Additionally, the letter strings 'Afre' and 'Atre' may appear similar when scripted. <u>Phonetic</u> Both names begin with the letter 'A', and can share a similar phonetic ending '-suh'. Additionally the names can be pronounced similarly (a-fres-uh vs. a-tres-suh) <u>Overlap in Numerical Values</u> Afrezza's dose can be written as 4 units of subcutaneous insulin. Atreza's strength is 0.4 mg <u>Frequency of Administration</u> Both products can be administered multiple times a day	The orthographic differences in the name, in addition to different product characteristics, minimize the likelihood of medication error in the usual practice setting. <u>Orthographic</u> The name Afrezza contains 7 letters whereas the name Atreza contains 6 letters, which makes Afrezza appear longer due to additional wide letter 'z' in the name. <u>Dosing Units</u> Afrezza is dosed in terms of units whereas Atreza is dosed in terms of mg. Additionally, Atreza is discontinued brand of atropine tablets. Although most prescribers order atropine by established name rather than a brand name, even if prescribers specifies the Atreza product and omits the strength, the prescriber will be including the ordered dose in terms of number of tablets or other dose descriptor, which will help the differentiation Atreza between Afrezza.

Oforta (Fludarabine) Tablets Strength 10 mg Usual Dose 25 mg/m^2 to 40 mg/m^2 Route of Administration Orally Frequency of Administration Once daily on days 1 though 5 every 4 weeks.	Orthographic Both names contain one upstroke in the beginning of the name. Additionally, the letter strings 'af-' and '-za' in the name Afrezza and may look similar to the corresponding letter strings 'of-' and '-ta' in the name Oforta. Numerical Overlap in Strength and Dose Afrezza may be prescribed in terms of strength such as Afrezza 10 units and in terms of achievable dose, such as Afrezza 40 units or Afrezza 50 units. Oforta's usual dose depends on the indication and person's BSA. Thus, Oforta's dose may be fluctuating. As a result, the overlap between Afrezza's strength or achievable dose and Oforta's strength and usual dose is possible.	The orthographic differences in the name, in addition to different product characteristics, minimize the likelihood of medication error in the usual practice setting. Orthographic Afrezza contains 7 letters and 2 upstrokes whereas Oforta contains 6 letters and 3 upstrokes. Additionally, the corresponding letter string '-rez-' in Afrezza and '-or-' in Oforta lack orthographic similarity when scripted. Dosing Units Afrezza is dosed in terms of units whereas Oforta is dosed in terms of mg. Frequency of Administration Afrezza should be administered at least three times a day (with each meal) whereas Oforta should be administered once daily for 5 days every 4 weeks

---

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

/s/

YELENA L MASLOV
12/10/2010

YELENA L MASLOV on behalf of ZACHARY A OLESZCZUK
12/10/2010

DENISE P TOYER
12/13/2010

Department of Health and Human Services

Public Health Service

Food and Drug Administration

Center for Drug Evaluation and Research

Office of Surveillance and Epidemiology

Date:	December 8, 2009
To:	Mary Parks, M.D., Director Division of Metabolism and Endocrine Products
Through:	Denise Toyer, PharmD, Deputy Director Carol Holquist, RPh, Director Division of Medication Error Prevention and Analysis, HFD-420
From:	Laura Pincock, RPh, PharmD, Acting Team Leader Division of Medication Error Prevention and Analysis, HFD-420
Subject:	Proprietary Name Review
Drug Name(s):	Afrezza (Insulin Inhalation Powder) 15 unit and 30 unit cartridges
Application Type/Number:	NDA 22472
Applicant/Applicant:	MannKind Corporation
OSE RCM #:	2009-1471

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

CONTENTS

EXECUTIVE SUMMARY

Afrezza is the proposed proprietary name for Insulin Inhalation Powder. This proposed name was evaluated from a safety and promotional perspective based on the product characteristics provided by the Applicant. We sought input from pertinent disciplines involved with the review of this application and considered it accordingly. Our evaluation did not identify concerns that would render the name unacceptable based on the product characteristics and safety profile known at the time of this review. Thus, DMEPA finds the proposed proprietary name Afrezza acceptable for this product. The proposed proprietary name must be re-reviewed 90 days before approval of the NDA.

Additionally, if any of the proposed product characteristics as stated in this review are altered, DMEPA rescinds this finding and the name must be resubmitted for review. The conclusions upon re-review are subject to change.

1 BACKGROUND

1.1 INTRODUCTION

This review is in response to a request from the Applicant for an assessment of the proposed proprietary name, Afrezza, regarding potential name confusion with other proprietary or established drug names in normal practice settings. The previous proposed proprietary name, Afresa, was found unacceptable in a previous review (OSE # 2007-2449, dated June 30, 2009) because our evaluation determined it was vulnerable to confusion with the currently marketed product Apidra. The Applicant has submitted a trademark safety evaluation from (b) (4) in support of the new proposed name, Afrezza. Labels and labeling for Afrezza will be reviewed in a forthcoming review.

1.2 PRODUCT INFORMATION

Afrezza is the proposed proprietary name for insulin inhalation powder delivered via a re-usable, breath-powered, high resistance, dry powder delivery device. Afrezza is intended for the treatment of adults with diabetes mellitus. Afrezza is proposed to be marketed in single dose cartridges of 15 units or 30 units. Per CMC, the 15 unit cartridge delivers 4 units of insulin and the 30 unit cartridge delivers 8 units of insulin. (b) (4)

(b) (4)

Insulin naïve patients should start on a dose of 15 units at each meal. For all other patients, the starting dose of Afrezza will be based on the total daily dose of subcutaneous insulin. Subjects will replace 50% of the total daily subcutaneous insulin dose with a corresponding dose of Afrezza divided between main meals, while the remaining 50% of total dose of subcutaneous insulin will be given as basal long-acting subcutaneous insulin. The prandial dose of Afrezza should be adjusted based on blood glucose levels.

Afrezza should be stored in the refrigerator (2-8˚C). (b) (4) The Afrezza inhaler can be used for up to one year from date of first use.

2 METHODS AND MATERIALS

This section describes the methods and materials used by DMEPA staff conducting a proprietary name risk assessment (see 2.1 Proprietary Name Risk Assessment). The primary focus for the assessment is to identify and remedy potential sources of medication error prior to drug approval. DMEPA defines a

medication error as any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer. [1]

2.1 PROPRIETARY NAME RISK ASSESSMENT

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

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

The Safety Evaluator assigned to the Proprietary Name Risk Assessment is responsible for considering the collective findings, and provides an overall risk assessment of the proposed proprietary name (see detail 2.1.2). The overall risk assessment is based on the findings of a Failure Mode and Effects Analysis (FMEA) of the proprietary name, and is focused on the avoidance of medication errors. FMEA is a systematic tool for evaluating a process and identifying where and how it might fail. [2] FMEA is used to analyze whether the drug names identified with look- or sound-alike similarity to the proposed name could cause confusion that subsequently leads to medication errors in the clinical setting. DMEPA uses the clinical expertise of the medication error staff to anticipate the conditions of the clinical setting that the product is likely to be used in based on the characteristics of the proposed product.

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

Typical product characteristics considered when identifying drug names that could potentially be confused with the proposed drug name include, but are not limited to established name of the proposed product, the proposed indication, dosage form, route of administration, strength, unit of measure, dosage units, recommended dose, typical quantity or volume, frequency of administration, product packaging, storage conditions, patient population, and prescriber population. Because drug name confusion can occur at any point in the medication use process, 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]

---

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

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

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

2.1.1 Search Criteria

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

For this review, particular consideration was given to drug names beginning with the letter 'A' when searching to identify potentially similar drug names, as 75% of the confused drug names reported by the USP-ISMP Medication Error Reporting Program involve pairs beginning with the same letter.[4,5]

To identify drug names that may look similar to Afrezza, DMEPA staff also considers the orthographic appearance of the name on lined and unlined orders. Specific attributes taken into consideration include the length of the name (seven letters), downstrokes (three, lower case letter 'f' and two letters 'z') and upstrokes (two, capital letter 'A' and lower case letter 'f'). Additionally, several letters in Afrezza may be vulnerable to ambiguity when scripted, including the capital letter 'A' may appear as capital letters 'C' or 'S'; lower case 'f' may look like lower case 'g' or 't' or 'p'; lower case 'r' may look like lower case 'n' or 'u' or 'm'; lower case letter 'e' may appear as lower case 'i' or 'e' or 'a'; lower case 'z' may appear as lower case 'p' or 'g' or 's'; and lower case 'a' may appear as lower case 'o', 'u', or 'i'. As such, DMEPA staff also considers these alternate appearances when identifying drug names that may look similar to Afrezza.

When searching to identify potential names that may sound similar to Afrezza, DMEPA staff search for names with similar number of syllables (3), stresses (uh-FRESS-uh, AF-re-zah, Af-re-ZAH or Af-REE-za, etc.), and placement of vowel and consonant sounds. Additionally, the DMEPA staff considers that pronunciation of parts of the name can vary such as "Afrezza" may be interpreted as 'A-fresa' or 'Afre-zah'. The Applicant's intended pronunciation of the proprietary name, Afrezza, was taken into consideration (uh-FRESS-uh) as it was included in the external proprietary name assessment. However, because names are often mispronounced and/or spoken with regional accents and dialects, other potential pronunciations of the names are considered.

The staff also consider the product characteristics associated with the proposed drug throughout the identification of similar drug names, since the product characteristics of the proposed drug ultimately determine the use of the product in the clinical practice setting For this review, DMEPA staff were provided with the following information about the proposed product: the proposed proprietary name (Afrezza), the proposed established name (insulin powder for inhalation), proposed indication (diabetes mellitus), strength (15 units, 30 units, or even 4 units or 8 units), dose (X units in increments of 4), frequency of administration (before or with meals, three times a day), route (oral), and dosage form (powder for inhalation). Appendix A provides a more detailed listing of the product characteristics that DMEPA staff generally take into consideration.

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

---

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

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

2.1.1.1 Database and Information Sources

The proposed proprietary name, Afrezza, was provided to DMEPA staff to conduct a search of the internet, several standard published drug product reference texts, and FDA databases to identify existing and proposed drug names that may sound-alike or look-alike to Afrezza using the criteria outlined in 2.1.1. A standard description of the databases used in the searches is provided in Section 7. To complement the process, DMEPA staff use a computerized method of identifying phonetic and orthographic similarity between medication names. The program, Phonetic and Orthographic Computer Analysis (POCA), uses complex algorithms to select a list of names from a database that have some similarity (phonetic, orthographic, or both) to the trademark being evaluated. Lastly, DMEPA staff review the USAN stem list to determine if any USAN stems are present within the proprietary name. The findings of the individual Safety Evaluators were then pooled and presented to the Expert Panel.

2.1.1.2 FDA Expert Panel Discussion

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

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

2.1.2 CDER Prescription Analysis Studies

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

In order to evaluate the potential for misinterpretation of Afrezza in handwriting and verbal communication of the name, inpatient medication orders and outpatient prescriptions are written, each consisting of a combination of marketed and unapproved drug products, including the proposed name. These orders are optically scanned and one prescription is delivered to a random sample of 123 participating health professionals via e-mail. In addition, a verbal prescription is recorded on voice mail. The voice mail messages are then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants send their interpretations of the orders via e-mail to DMEPA staff.

Figure 1. Afrezza Study (conducted on October 5, 2009)

HANDWRITTEN REQUISITION MEDICATION ORDER	VERBAL PRESCRIPTION
Inpatient Medication Order: Afrezza 12 units before each meal	" Afrezza, 12 units before each meal"
Outpatient Prescription: Afrezza 8 units AC	

2.1.3 Comments from the Division of Metabolism and Endocrine Products (DMEP))

DMEPA requests the regulatory division in the Office of New Drugs responsible for the application for their comments and/or clinical/other concerns on the proposed proprietary name at the initial phase of the name review. Additionally, when applicable, at the same time DMEPA requests concurrence/non-concurrence with DDMAC's decision on the name. Any comments or concerns are addressed in the safety evaluator's assessment.

The Review Division is contacted a second time following our analysis of the proposed name. At this point, DMEPA conveys their decision to accept or reject the name. The regulatory division is requested to concur /not concur with DMEPA's final decision.

2.1.4 External Proprietary Name Risk Assessment

For this product, the Applicant submitted an external evaluation of the proposed proprietary name, Afrezza. The Division of Medication Error Prevention and Analysis conducts an independent analysis and evaluation of the data provided, and responds to the overall findings of the assessment. When the external proprietary name risk assessment identifies potentially confusing names that were not captured in DMEPA's database searches or in the Expert Panel Discussion, these names are included in the Safety Evaluator's Risk Assessment and analyzed independently by the Safety Evaluator to determine if the potentially confusing name could lead to medication errors in usual practice settings.

After the Safety Evaluator has determined the overall risk assessment of the proposed name, the Safety Evaluator compares the findings of their overall risk assessment with the findings of the proprietary name risk assessment submitted by the Applicant. The Safety Evaluator then determines whether the Division's risk assessment concurs or differs with the findings.

2.1.5 Safety Evaluator Risk Assessment of the Proposed Proprietary Name

Based on the criteria set forth in Section 2.1, the Safety Evaluator Risk Assessment applies their individual expertise gained from evaluating medication errors reported to FDA to conduct a Failure Mode and Effects Analysis and provide an overall risk of name confusion. Failure Mode and Effects Analysis (FMEA) is a systematic tool for evaluating a process and identifying where and how it might fail.[6] When applying FMEA to assess the risk of a proposed proprietary name, DMEPA seeks to evaluate the potential for a proposed name to be confused with another drug name as a result of the name confusion and cause errors to occur in the medication use system. FMEA capitalizes on the predictable and preventable nature of medication errors associated with drug name confusion. FMEA allows the Agency to identify the potential for medication errors due to look- or sound-alike drug names prior to approval, where actions to overcome these issues are easier and more effective then remedies available in the post-approval phase.

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

In the initial stage of the Risk Assessment, the Safety Evaluator compares the proposed proprietary name to all of the names gathered from the above searches, expert panel evaluation, and studies, and identifies potential failure modes by asking: "Is the name Afrezza convincingly similar to another drug name, which may cause practitioners to become confused at any point in the usual practice setting?" An affirmative answer indicates a failure mode and represents a potential for Afrezza to be confused with another proprietary or established drug name because of look- or sound-alike similarity. If the answer to the question is no, the Safety Evaluator is not convinced that the names posses similarity that would cause confusion at any point in the medication use system and the name is eliminated from further review.

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

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

1. DDMAC finds the proposed proprietary name misleading from a promotional perspective, and the review Division concurs with DDMAC's findings. The Federal Food, Drug, and Cosmetic Act provides that labeling or advertising can misbrand a product if misleading representations are

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

made or suggested by statement, word, design, device, or any combination thereof, whether through a trade name or otherwise. [21 U.S.C 321(n); see also 21 U.S.C. 352(a) & (n)].

2. DMEPA identifies that the proposed proprietary name is misleading because of similarity in spelling or pronunciation to another proprietary or established name of a different drug or ingredient [CFR 201.10.(C)(5)].
3. FMEA identifies potential for confusion between the proposed proprietary name and other proprietary or established drug names, and demonstrates that medication errors are likely to result from the drug name confusion under the conditions of usual clinical practice.
4. The proposed proprietary name contains an USAN stem, particularly in a manner that is contradictory to the USAN Council's definition.
5. DMEPA staff identify a potential source of medication error within the proposed proprietary name. The proprietary name may be misleading, or inadvertently introduce ambiguity and confusion that leads to errors. Such errors may not necessarily involve confusion between the proposed drug and another drug product.

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 is awarded approval first has the right to the use the name, while DMEPA will recommend that the second product to reach approval seek an alternative name.

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

Furthermore, 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, can be identified and remedied prior to approval to avoid patient harm.

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

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

plausible strategies that could reduce the risk of medication error of the currently proposed name, and so DMEPA may be able to provide the Applicant with recommendations that reduce or eliminate the potential for error would render the proposed name acceptable.

3 RESULTS

3.1 PROPRIETARY NAME RISK ASSESSMENT

3.1.1 Database and Information Sources

The search of the internet, several standard published databases and information sources (see Section 7 References) yielded a total of 17 names as having some similarity to the name Afrezza.

Thirteen of the 17 names were thought to look like Afrezza. These include Abreva, Aflexa, Alenaze D, Apriso, Akurza, Albenza, Avinza, Afrinol, Afrazine, Allegra, Strattera, Cefizox, and Arzerra. One of the 17 names were thought to sound like Afrezza (Iressa). The remaining three names were thought to look and sound similar to Afrezza (Afresa***, Atreza, (b) (4)

Additionally, we did not identify any United States Adopted Names (USAN) stems in the name, Afrezza, as of October 18, 2009.

3.1.2 Expert Panel Discussion

The Expert Panel reviewed the pool of names identified by DMEPA staff (see section 3.1.1. above) and noted no additional names thought to have orthographic or phonetic similarity to Afrezza. DDMAC had no concerns regarding the proposed name from a promotional perspective, and did not offer any additional comments relating to the proposed name.

3.1.3 FDA Prescription Analysis Studies

A total of 22 practitioners responded. One of the five respondents for the inpatient written study interpreted the name as 'Abreva', a product that is currently marketed (see Appendix H). None of the remaining responses overlapped with any existing or proposed drug names. In the verbal studies, all responses were misspelled phonetic variations of the proposed name, 'Afrezza' (n=3). See Appendix B for the complete listing of interpretations from the verbal and written prescription studies.

3.1.4 External Proprietary Name Risk Assessment

In the proposed name risk assessment submitted by the Applicant, (b) (4) identified and evaluated a total of 2 drug names thought to have some potential for confusion with the name Afrezza. Both names were previously identified in our staff searches (Iressa and Abreva). Iressa was identified as having sound-alike similarity to Afrezza, and Abreva was identified as having look-alike similarity to Afrezza. (b) (4) concluded that despite some safety concerns, (b) (4) believes that trademark Afrezza can safely co-exist in the market for which it was tested.

3.1.5 Safety Evaluator Risk Assessment

Independent searches by the Safety Evaluator identified five additional names that were thought to look or sound similar to Afrezza and represent a potential source of name confusion. The names are Cyclessa, Alesse, (b) (4) Apidra, and Atripla.

Therefore, a total of 22 names were analyzed to determine if the drug names could be confused with Afrezza and represent a potential source of drug name confusion.

Failure mode and effect analysis was then applied to determine if the potential name, Afrezza, could potentially be confused with any of the 22 names and lead to medication errors. This analysis determined that the name similarity between Afrezza and the identified names was unlikely to result in medication errors with all 22 products identified for the reasons presented in Appendicies C-H.

3.1.6 Comments from the Division of Metabolism and Endocrine Products (DMEP)

DMEP concurred with the assessment of the safety concerns and objection expressed by DMEPA in an email dated December 1, 2009. Additionally, DMEP did not have any other comments and/or clinical/other concerns on the proposed proprietary name.

4 DISCUSSION

4.1 PROPRIETARY NAME RISK ASSESSMENT

Neither DDMAC nor the review Division had concerns with the proposed name.

DMEPA identified and evaluated twenty-two names for their potential similarity to the proposed name, Afrezza. Six names lacked orthographic and/or phonetic similarity and were not evaluated further (see Appendix C).

Failure mode and effect analysis (FMEA) was then applied to determine if the potential name could potentially be confused with the remaining sixteen names and lead to medication errors. This analysis determined that the name similarity between Afrezza and the remaining sixteen products was unlikely to result in medication errors for the reasons presented in Appendices D through H.

Additionally, DMEPA did not identify any other factors outside of identifying potentially similar or promotional names that would render the name unacceptable at this time. This finding is consistent with the independent name study.

5 CONCLUSIONS AND RECOMMENDATIONS

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

However, if any of the proposed product characteristics as stated in this review are altered, DMEPA rescinds this Risk Assessment finding and the name must be resubmitted for review. In the event that our Risk Assessment finding is rescinded, the evaluation of the name on resubmission is independent of the previous Risk Assessment, and as such, the conclusions on re-review of the name are subject to change. The proposed name must be re-reviewed 90 days before approval of the NDA. For questions or clarifications, please contact OSE Project Manager Millie Wright, at 301-796-4053.

5.1 COMMENTS TO THE APPLICANT

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

The proprietary name, Afrezza, will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you.

6 REFERENCES

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

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

2. Phonetic and Orthographic Computer Analysis (POCA)

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

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

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

4. AMF Decision Support System [DSS]

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

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

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

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

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

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

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

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

Provides information regarding patent and trademarks.

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

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

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

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

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

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

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

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

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

List contains all the recognized USAN stems.

14. Red Book Pharmacy's Fundamental Reference

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

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

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

16. Medical Abbreviations Book

Contains commonly used medical abbreviations and their definitions.

APPENDICES

Appendix A:

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

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

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

Appendix B: **CDER Prescription Study Responses**

Inpatient Medication Order	Outpatient Medication Order	Voice Prescription
Abrerra (possibly Afrerra, looks similar to Abreva)	Affrezzor	Affressa
Abreva	Afrezza	Afresa
Abrena	Atrizza	Afreza
Afrerra	Afrenza	
Abrerra	Afrenza	
Afrena	Afrezza	
	Afrezzor	
	Afrezza	
	Afrezza	
	Afresza	
	Affrezzor	
	Afrezza	
	Afrezza	
	Afreyza	

Appendix C: Names Lacking Orthographic and/or Phonetic Similarity.

Name	Name
Alenaze D	Allegra
Afrinol	Strattera
(b) (4)	Alesse

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

Appendix D: Product names that have not ever been marketed

Proprietary Name	Similarity to Afrezza	Status of product name
Afresa* **	Look and Sound	Proposed name for this same product that was found unacceptable in a previous review (OSE # 2007-2449, dated June 30, 2009) because our evaluation determined it was vulnerable to confusion with the currently marketed product Apidra. Therefore the name Afresa*** is no longer under consideration for use as a proprietary name of a drug product.
(b) (4) **(Desogestrel and Ethinyl estradiol)**		Proposed name for this generic product was not recommended in a previous review (OSE # 04-0094, dated May 19, 2004) because of the sponsor's proposals for (b) (4) and concerns about the possibility of errors resulting from confusion from the proliferation of those suffixes. ANDA # 76916 was approved December 29, 2008 without a proprietary name.
***** This document contains proprietary and confidential information that should not be released to the public.*****		

Appendix E: Products marketed in foreign countries

Proprietary Name	Similarity to Afrezza
Afrazine (oxymetazoline in United Kingdom and Ireland)	Look

Appendix F: Products with no overlap in strength or dose

Product name with potential for confusion	Similarity to Afrezza	Strength	Usual Dose (if applicable)
Afrezza	**N/A**	**15 units or 30 units**	**Given with meals (three times a day). Cartridge delivers 4 units (15 unit strength) or 8 units (30 unit strength) via** (b) (4) **Patient may also be ordered concomitant long-acting subcutaneous insulin.**
Akurza **(salicylic acid)**	Look	Topical cream: 6% (340 g) Topical lotion: 6% (355 mL)	Apply to affected area once daily, generally used at night and rinsed off in the morning.
Cefizox **(Ceftizoxime)**	Look	Infusion [premixed]: 1 g (50 mL), 2 g (50 mL) Injection, powder for reconstitution: 1 g, 2 g	*Adults:* The usual dose is 500 mg, 1 g, or 2 g via intramuscular injection or intravenous infusion over 30 minutes every 8 to 12 hours, depending on the severity of infection and organism susceptibility. Life-threatening infections may require 3 to 4 g every 8 hours.

Appendix G: Single strength products with multiple differentiating product characteristics

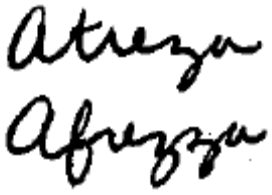
Product name with potential for confusion	**Similarity to Afrezza**	**Strength**	**Usual Dose (if applicable)**	**Differentiating Product Characteristics (Afrezza vs. Product)**
Afrezza	**N/A**	**15 units or 30 units**	**Given with meals (three times a day). Cartridge delivers 4 units (15 unit strength) or 8 units (30 unit strength) via** (b) (4) **Patient may also be ordered concomitant long-acting subcutaneous insulin.**	**N/A**
Aflexa **(glucosamine)** nonprescription dietary supplement	Look and Sound	Tablets: 340 mg	In clinical studies of arthritis, glucosamine dosage has typically been 1.5 g/day, as a single dose or in divided doses.	Strength (340 mg vs. 4 units, 8 units, 15 units or 30 units) Dose (340 mg or 1 tablet vs. X units) Dosage form (tablet vs. powder for inhalation) Route of administration (oral vs. inhalation) Indication (osteoarthritis vs. diabetes) Non-prescription vs. prescription status

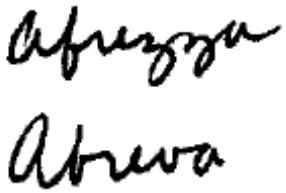
Product name with potential for confusion	**Similarity to Afrezza**	**Strength**	**Usual Dose (if applicable)**	**Differentiating Product Characteristics (Afrezza vs. Product)**
Afrezza	**N/A**	**15 units or 30 units**	**Given with meals (three times a day). Cartridge delivers 4 units (15 unit strength) or 8 units (30 unit strength) via** (b) (4) [redacted] **Patient may also be ordered concomitant long-acting subcutaneous insulin.**	**N/A**
Iressa **(gefitinib)** Note: In response to the lack of improved survival data from the ISEL trial, AstraZeneca has temporarily suspended promotion of this drug.	Sound	Tablet: 250 mg	250 mg/day; consider 500 mg/day in patients receiving effective CYP3A4 inducers (e.g., rifampin, phenytoin)	Strength (250 mg vs. 4 units, 8 units, 15 units or 30 units) Dose (250 mg or 1 tablet vs. X units) Dosage form (tablet vs. powder for inhalation) Route of administration (oral vs. inhalation) Frequency of administration (once daily vs. three times daily with meals) Indication for use (oncology vs. diabetes)

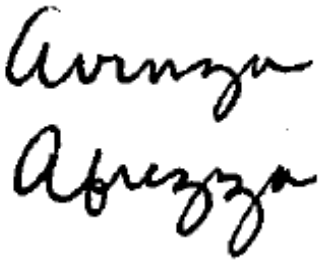
Product name with potential for confusion	Similarity to Afrezza	Strength	Usual Dose (if applicable)	Differentiating Product Characteristics (Afrezza vs. Product)
Afrezza	**N/A**	**15 units or 30 units**	**Given with meals (three times a day). Cartridge delivers 4 units (15 unit strength) or 8 units (30 unit strength) via** (b) (4) [redacted] **Patient may also be ordered concomitant long-acting subcutaneous insulin.**	**N/A**
Albenza **(albendazole)**	Look	Tablets: 200 mg	**Neurocysticercosis:** Oral: <60 kg: 15 mg/kg/day in 2 divided doses (maximum: 800 mg/day) for 8-30 days ≥60 kg: 800 mg/day in 2 divided doses for 8-30 days **Note:** Give concurrent anticonvulsant and steroid therapy during first week. **Hydatid:** Oral: <60 kg: 15 mg/kg/day in 2 divided doses (maximum: 800 mg/day) ≥60 kg: 800 mg/day in 2 divided doses **Note:** Administer dose for three 28-day cycles with a 14-day drug-free interval in between. The manufacturer recommends a total of 3 cycles. ***Ancylostoma caninum*, *Ascaris lumbricoides* (roundworm)**, ***Ancylostoma duodenale* (*hookworm*):** Oral: 400 mg as a single dose	Strength (200 mg vs. 4 units, 8 units, 15 units or 30 units) Dose (200 mg, 400 mg, 1 tablet, or 2 tablets vs. X units) Dosage form (tablet vs. powder for inhalation) Route of administration (oral vs. inhalation) Indication for use (antihelminthic vs. diabetes)

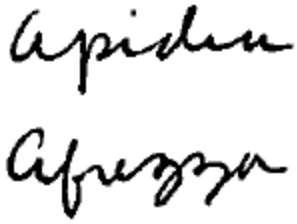
Product name with potential for confusion	Similarity to Afrezza	Strength	Usual Dose (if applicable)	Differentiating Product Characteristics (Afrezza vs. Product)
Afrezza	**N/A**	**15 units or 30 units**	**Given with meals (three times a day). Cartridge delivers 4 units (15 unit strength) or 8 units (30 unit strength) via** (b) (4) [redacted] **Patient may also be ordered concomitant long-acting subcutaneous insulin.**	**N/A**
Atripla (Efavirenz, Emtricitabine, and Tenofovir)	Look	Tablet: 600 mg/ 200 mg/300 mg	One tablet orally once a day	Dose (1 tablet vs. X units) Dosage form (tablet vs. powder for inhalation) Route of administration (oral vs. inhalation) Frequency of administration (once daily vs. three times daily with meals) Indication for use (HIV/AIDS vs. diabetes)
Cyclessa (Desogestrel and Ethinyl Estradiol)	Sound	Varying strengths (oral contraceptive pack)	One tablet orally once a day Day 1-7: Ethinyl estradiol 0.025 mg and desogestrel 0.1 mg [7 light yellow tablets] Day 8-14: Ethinyl estradiol 0.025 mg and desogestrel 0.125 mg [7 orange tablets] Day 14-21: Ethinyl estradiol 0.025 mg and desogestrel 0.15 mg [7 red tablets] Day 21-28: 7 green inactive tablets (28s)	Dose (1 tablet vs. X units) Dosage form (tablet vs. powder for inhalation) Route of administration (oral vs. inhalation) Frequency of administration (once daily vs. three times daily with meals) Indication for use (birth control vs. diabetes)

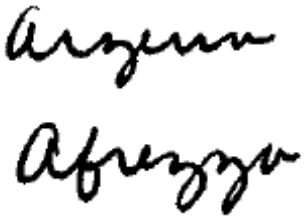
Appendix H Products with a potentially confusing name, *but medication error is unlikely to result from confusion of the name pair.*

Afrezza **(insulin inhalation powder)**	**15 units or 30 units**	**Given with meals (three times a day). Cartridge delivers 4 units (15 unit strength) or 8 units (30 unit strength) via** (b) (4) **Patient may also be ordered concomitant long-acting subcutaneous insulin.**
Failure Mode: **Name confusion**	**Causes** **(could be multiple)**	**Effects**
Atreza **(atropine sulfate)** Tablets: 0.4 mg Pre-operative use: 2 mg orally 30-60 min prior to anesthesia GI disorders: 0.3-1.2 mg orally every 4 to 6 hours Atreza brand is no longer marketed although generics are available. This was confirmed with Hawthorn Pharmaceuticals in a phone call 11/16/09.	Orthographic similarity: ('At-' vs. 'Af-') may appear similar when scripted; similar endings ('-za' vs. '-zza')  Phonetic similarity: Both names begin with an 'A', and they can share a similar phonetic ending '-suh'. The names can be pronunced similarly (a-tres-suh vs. a-fres-uh) when spoken.	Orthographic differences in the names minimize the likelihood of medication errors in the usual practice setting. Specifically, the three downstrokes from the letter 'f' and the two letters 'z' in Afrezza compared to a single downstroke from the letter 'z' in Atreza helps to differentiate the names. *Rationale:* Atreza is a different dosage form (tablet) than Afrezza (powder for inhalation). Both products are administered several times a day, with Atreza given pre-operatively or every 4 to 6 hours, and Afrezza administered three times a day with meals. Atreza is available in a single strength, so the strength (0.4 mg) may be omitted on a prescription, however, the prescription will contain additional information that can help differentiate an Atreza prescription, such as number of tablets, the mg dose ordered, or a dosing frequency in hours. Additionally, Atreza is a discontinued brand of atropine sulfate tablets. Although most prescribers order atropine by the established name rather than a brand name, even if a prescriber specifies the Atreza product and omits the strength, the prescriber will be including the ordered dose in terms of number of tablets or other dose descriptor along with a frequency of use that will differentiate between a prescription for Atreza and Afrezza. Thus due to orthographic differences, as well as differences in the dosage formulation, route of delivery, and any other instructions for use, DMEPA believes it is unlikely that a medication error will occur.

Abreva **(docusanol)** non-prescription Cream, topical: 10% (2 g) Apply 5 times/day to affected area of face or lips. Start at first sign of cold sore or fever blister and continue until healed.	Orthographic similarity: ('Ab-' vs. 'Af-') may appear similar when scripted; similar endings ('-va' vs. '-zza') 	Orthographic differences in the names minimize the likelihood of medication errors in the usual practice setting. Although the letter 'b' in Abreva and the letter 'f' in Afrezza can look similar when scripted, the differences between the letter 'v' in Abreva and the letters 'zz' in Afrezza, especially the downstrokes, can help to differentiate the names. *Rationale:* Abreva is a different dosage form (topical cream) than Afrezza (insulin powder for inhalation) with a different route of administration. Abreva is applied five times a day on an intermittent basis when a cold sore appears until it heals. Afrezza will be used on an ongoing basis, three times a day before meals to treat a chronic disease (diabetes). Abreva is available in a single strength (10%) and is a non-prescription product. Thus an order for Abreva that lacks a strength, such as "Abreva, dispense 1" could be seen. However, there may be additional directions for use on a Abreva prescription such as "apply to sores until healed." Prescriptions for Afrezza will contain a dose in units of insulin or number of cartridges. There are also likely to be additional directions for use on an Afrezza prescription, such as "use three times a day before meals' or something similar. This additional information on prescriptions for Abreva/Afrezza will decrease the potential for confusion between the two names. Thus, due to orthographic differences, as well as differences in the dosage formulation, directions for use, and route of delivery, DMEPA believes it is unlikely that a medication error will occur.

Apriso **(mesalamine)** Look Capsule, delayed and extended release: 0.375 g 1.5 g (4 capsules) orally once daily in the morning	Orthographic similarity: Both names start with the letter 'A'; similar endings ('-so' vs. '-zza')  Overlapping numerical dose: the Apriso dose may be ordered as 4 capsules and the Afrezza 15 unit cartridge delivers 4 units of insulin. Thus the Afrezza dose could be ordered as 4 units on a prescription.	Orthographic differences in the names minimize the likelihood of medication errors in the usual practice setting. Specifically, the letter 'p' in Apriso is noticeable when scripted and the letter 'i' (when dotted) helps to differentiate the names. The two downstrokes from the letters 'zz' in Afrezza also help to differentiate the names. *Rationale:* Apriso is a different dosage form (capsule) than Afrezza (powder for inhalation). Apriso is administered once daily in the morning, whereas Afrezza is administered three times a day with meals. Apriso is available in a single strength, so the strength (0.375 mg) may be omitted on a prescription, however, the prescription would need to contain a dose (e.g., 1.5 g) or number of capsules (e.g., 4) to be dispensed. A prescription for Afrezza would contain the dose in units of insulin or number of cartridges. Although there is an overlap with the number 4, there should be accompanying units of measure (capsules for Apriso and units of insulin or number of cartridges for Afrezza) on the prescription, as well as additional instructions for use (e.g., three times a day before meals), that may help differentiate the names. Thus due to orthographic differences, as well as differences in the dosage formulation, route of delivery, and any other instructions for use, DMEPA believes the risk is low that a medication error will occur with this name pair.
Avinza **(morphine sulfate)** Look Extended-release capsules: 30 mg, 45 mg, 60 mg, 75 mg, 90 mg, 120 mg Daily dose is converted from immediate release morphine dose and is titrated and	Orthographic similarity: ('Av-' vs. 'Af-') may appear similar when scripted; identical endings ('-za')  Overlapping numerical strength:	Orthographic differences in the names minimize the likelihood of medication errors in the usual practice setting. Specifically, the three downstrokes from the letters 'f' and 'zz' in Afrezza when compared to one downstroke in the name Avinza help to differentiate the names. *Rationale:* Avinza is a different dosage form (capsule) than Afrezza (powder for inhalation). Avinza is administered once daily at the same time each day, whereas Afrezza is administered three times a day with meals.

administered once daily (for best results, administer at same time each day).	30 mg (Avinza) vs. 30 units (Afrezza)	Both Avinza and Afrezza are available in overlapping numerical strengths of 30 mg and 30 units, respectively. Therefore, a pharmacist would rely on the measuring unit (mg or units) and the additional instructions for use when dispensing a prescription written for Avinza/Afrezza. The additional instructions for use of each drug are very different and may help to differentiate the names. For example, Avinza 30 mg may be 'take one capsule each day' and Afrezza 30 units may be 'inhale 8 units before each meal'. Thus due to orthographic differences, as well as differences in the dosage formulation, route of delivery, and any other instructions for use, DMEPA believes it is unlikely that a medication error will occur with this name pair.
Apidra **Apidra OptiClik** **(insulin glulisine)** Apidra: 100 units/mL (10 mL) Apidra OptiClik: 100 units/mL (15 mL)	Orthographic similarity: ('Ap-' vs. 'Af-') may appear similar when scripted; similar endings ('-zza' vs. '-sa')  Products share indications and patient populations; both are insulins and used for treatment in diabetes. Overlapping or identical doses: both products are dosed in units of insulin	Orthographic differences in the names minimize the likelihood of medication errors in the usual practice setting. The upstroke from the letter 'd' in Apidra and the two downstrokes from the letters 'zz' in Afrezza, contained in the same general location of both names, help to differentiate the names. Apidra is a different dosage form (insulin glulisine for injection) than Afrezza (insulin powder for inhalation) with a different route of delivery. However, both Apidra and Afrezza share indications and patient populations; both are insulins and used for treatment in diabetes. Thus a pharmacist can dispense either product to a patient that is known to have diabetes and require insulin treatment. As both Apidra and Afrezza are insulin preparations, they will have overlapping numerical doses (in units) that can increase the potential for confusion. Both will be administered as rapid acting insulin for diabetic patients to take just prior to meals. Both products will be used on a chronic and ongoing basis. However, we believe the orthographic differences are adequate to differentiate the products. Additionally, the use of Afrezza and Apidra each require individual patient training on the proper preparation and administration of the prescribed product. In the unlikely event that an order for Abreva/Afresa is misinterpreted and the patient gets the wrong product, the patient will recognize the error due to the product differences and

		packaging from what they were expecting: the Afresa inhaler/cartridges versus the Apidra vial or pen.
Arzerra **(ofatumumab)**	Orthographic similarity: ('Arz-') and ('Afr-') may appear similar when scripted and both names end with the letter 'a'.  Overlapping numerical dose/strengths: 300 mg is the initiation dose for Arzerra and 30 units is the strength for Afrezza Arzerra recommended dose and schedule: 300 mg initial dose (Dose 1) followed by 2 g weekly for 7 doses (Doses 2-8) followed 4 weeks later by 2g every 4 weeks for 4 doses (Doses 9-12) Arzerra was recently approved by FDA on October 26, 2009	Orthographic differences in the names minimize the likelihood of medication errors in the usual practice setting. The downstroke from the letter 'z' in Arzerra and the two downstrokes from the letters 'zz' in Afrezza, are in different locations of the names and help to differentiate the names. Arzerra is a different dosage form (injection for intravenous infusion) than Afrezza (insulin powder for inhalation) with a different route of delivery. Arzerra is administered on a weekly or monthly (every 4 weeks) basis as part of a prescribed chemotherapeutic regimen, whereas Afrezza is administered three times a day with meals. Both Arzerra and Afrezza are available in overlapping numerical dose/strengths of 300 mg and 30 units, respectively. Therefore, a pharmacist would rely on the measuring unit (mg or units) and the additional instructions for use when dispensing a prescription written for Arzerra/Afrezza. The additional instructions for use of each drug are very different and may help to differentiate the names. For example, Arzerra 300 mg, the single initial dose of the weekly regimen may be 'infuse at 3.6 mg/hour (25 mL/hr)' and Afrezza 30 units may be 'inhale 8 units before each meal'. Furthermore, because Arzerra is part of a chemotherapeutic regimen, orders for Arzerra will be written on an inpatient or chemotherapeutic order form for dosing in an infusion clinic or inpatient setting. Thus due to orthographic differences, as well as differences in the dosage formulation, route of delivery, the setting for use of Arzerra, and any other instructions for use, DMEPA believes it is unlikely that a medication error will occur with this name pair.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22472	ORIG-1	MANNKIND CORP	INSULIN HUMAN (RDNA ORIG)INH POWDER

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

/s/

LAURA L PINCOCK
12/08/2009

DENISE P TOYER
12/08/2009

CAROL A HOLQUIST
12/08/2009

Department of Health and Human Services

Public Health Service

Food and Drug Administration

Center for Drug Evaluation and Research

Office of Surveillance and Epidemiology

Date:	June 30, 2009
To:	Mary Parks, M.D., Director Division of Metabolism and Endocrine Products
Through:	Denise Toyer, PharmD, Deputy Director Carol Holquist, RPh, Director Division of Medication Error Prevention and Analysis, HFD-420
From:	Laura Pincock, RPh, PharmD, Acting Team Leader Division of Medication Error Prevention and Analysis, HFD-420
Subject:	Proprietary Name Review
Drug Name(s):	Afresa (Insulin Inhalation Powder) 15 unit and 30 unit cartridges
Application Type/Number:	NDA 22-472
Applicant/Applicant:	MannKind Corporation
OSE RCM #:	2007-2449

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

CONTENTS

EXECUTIVE SUMMARY

Afresa is the proposed proprietary name for Insulin Inhalation Powder. This proposed name was evaluated from a safety and promotional perspective based on the product characteristics provided by the Applicant. We sought input from pertinent disciplines involved with the review of this application and considered it accordingly. Our evaluation determined that the proposed proprietary name, Afresa is unacceptable because it is similar in product characteristics and appearance to the currently marketed product Apidra and thus vulnerable to confusion (see Section 5). The Applicant will be notified that we found the proposed name Afresa unacceptable and will be requested to submit an alternate name for review.

1 BACKGROUND

1.1 INTRODUCTION

This review is in response to a request from the Applicant for an assessment of the proposed proprietary name, Afresa, regarding potential name confusion with other proprietary or established drug names in normal practice settings. Labels and labeling will be reviewed in a forthcoming review.

1.2 PRODUCT INFORMATION

Afresa is the proposed proprietary name for insulin inhalation powder delivered via a re-usable, breath-powered, high resistance, dry powder delivery device. Afresa is intended for the treatment of adults with diabetes mellitus. Afresa is proposed to be marketed in single dose cartridges of 15 units or 30 units. Per CMC, the 15 unit cartridge delivers 4 units of insulin and the 30 unit cartridge delivers 8 units of insulin.

(b) (4)

Insulin naïve patients should start on a dose of 15 units at each meal. For all other patients, the starting dose of Afresa will be based on the total daily dose of subcutaneous insulin. Subjects will replace 50% of the total daily subcutaneous insulin dose with a corresponding dose of Afresa divided between main meals, while the remaining 50% of total dose of subcutaneous insulin will be given as basal long-acting subcutaneous insulin. The prandial dose of Afresa should be adjusted based on blood glucose levels.

Afresa should be stored in the refrigerator (2-8 °C). (b) (4) The Afresa inhaler can be used for up to one year from date of first use.

2 METHODS AND MATERIALS

This section describes the methods and materials used by DMEPA staff conducting a proprietary name risk assessment (see 2.1 Proprietary Name Risk Assessment). The primary focus for the assessment is to identify and remedy potential sources of medication error prior to drug approval. 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]

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

2.1 PROPRIETARY NAME RISK ASSESSMENT

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

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

The Safety Evaluator assigned to the Proprietary Name Risk Assessment is responsible for considering the collective findings, and provides an overall risk assessment of the proposed proprietary name (see detail 2.1.2). The overall risk assessment is based on the findings of a Failure Mode and Effects Analysis (FMEA) of the proprietary name, and is focused on the avoidance of medication errors. FMEA is a systematic tool for evaluating a process and identifying where and how it might fail. [2] FMEA is used to analyze whether the drug names identified with look- or sound-alike similarity to the proposed name could cause confusion that subsequently leads to medication errors in the clinical setting. DMEPA uses the clinical expertise of the medication error staff to anticipate the conditions of the clinical setting that the product is likely to be used in based on the characteristics of the proposed product.

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

Typical product characteristics considered when identifying drug names that could potentially be confused with the proposed drug name include, but are not limited to established name of the proposed product, the proposed indication, dosage form, route of administration, strength, unit of measure, dosage units, recommended dose, typical quantity or volume, frequency of administration, product packaging, storage conditions, patient population, and prescriber population. Because drug name confusion can occur at any point in the medication use process, 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]

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

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

2.1.1 Search Criteria

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

For this review, particular consideration was given to drug names beginning with the letter 'A' when searching to identify potentially similar drug names, as 75% of the confused drug names reported by the USP-ISMP Medication Error Reporting Program involve pairs beginning with the same letter.[4,5]

To identify drug names that may look similar to Afresa, DMEPA staff also considers the orthographic appearance of the name on lined and unlined orders. Specific attributes taken into consideration include the length of the name (seven letters), and upstrokes (two, capital letter 'A' and lower case letter 'f'). Additionally, several letters in Afresa may be vulnerable to ambiguity when scripted, including the capital letter 'A' may appear as capital letters 'C' or 'S'; lower case 'f' may look like lower case 'g' or 't' or 'p'; lower case 'r' may look like lower case 'n' or 'u' or 'm'; lower case letter 'e' may appear as lower case 'i' or 'e' or 'a'; lower case 's' may appear as lower case 'a'; and lower case 'a' may appear as lower case 'o', 'u', or 'i'. As such, DMEPA staff also considers these alternate appearances when identifying drug names that may look similar to Afresa.

When searching to identify potential names that may sound similar to Afresa, DMEPA staff search for names with similar number of syllables (3), stresses (uh-FRESS-uh, AF-re-zah or Af-REE-za, etc.), and placement of vowel and consonant sounds. Additionally, the DMEPA staff considers that pronunciation of parts of the name can vary such as "Afresa" may be interpreted as 'A-fresa' or 'Afre-zah'. The Applicant's intended pronunciation of the proprietary name, Afresa, was taken into consideration (uh-FRESS-uh) as it was included in the external proprietary name assessment. However, because names are often mispronounced and/or spoken with regional accents and dialects, other potential pronunciations of the names are considered.

The staff also consider the product characteristics associated with the proposed drug throughout the identification of similar drug names, since the product characteristics of the proposed drug ultimately determine the use of the product in the clinical practice setting For this review, DMEPA staff were provided with the following information about the proposed product: the proposed proprietary name (Afresa), the proposed established name (insulin powder for inhalation), proposed indication diabetes mellitus), strength (15 units, 30 units or even 4 units or 8 units), dose (varying units), frequency of administration (with meals [three times a day]), route (oral), and dosage form (powder for inhalation). Appendix A provides a more detailed listing of the product characteristics that DMEPA staff generally take into consideration.

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

---

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

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

2.1.1.1 Database and Information Sources

The proposed proprietary name, Afresa, was provided to DMEPA staff to conduct a search of the internet, several standard published drug product reference texts, and FDA databases to identify existing and proposed drug names that may sound-alike or look-alike to Afresa using the criteria outlined in 2.1.1. A standard description of the databases used in the searches is provided in Section 7. To complement the process, DMEPA staff use a computerized method of identifying phonetic and orthographic similarity between medication names. The program, Phonetic and Orthographic Computer Analysis (POCA), uses complex algorithms to select a list of names from a database that have some similarity (phonetic, orthographic, or both) to the trademark being evaluated. Lastly, DMEPA staff review the USAN stem list to determine if any USAN stems are present within the proprietary name. The findings of the individual Safety Evaluators were then pooled and presented to the Expert Panel.

2.1.1.2 FDA Expert Panel Discussion

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

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

2.1.2 CDER Prescription Analysis Studies

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

In order to evaluate the potential for misinterpretation of Afresa in handwriting and verbal communication of the name, inpatient medication orders and outpatient prescriptions are written, each consisting of a combination of marketed and unapproved drug products, including the proposed name. These orders are optically scanned and one prescription is delivered to a random sample of 123 participating health professionals via e-mail. In addition, a verbal prescription is recorded on voice mail. The voice mail messages are then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants send their interpretations of the orders via e-mail to DMEPA staff.

Figure 1. Afresa Study (conducted on May 11, 2009)

HANDWRITTEN REQUISITION MEDICATION ORDER	VERBAL PRESCRIPTION
Inpatient Medication Order: Afresa inhale 4unit with every meals	" Afresa, inhale 4 units with every meal "
Outpatient Prescription: Afresa inhale 4 units with meals	

2.1.3 Comments from the Division of Metabolism and Endocrine Products (DMEP))

DMEPA requests the regulatory division in the Office of New Drugs responsible for the application for their comments and/or clinical/other concerns on the proposed proprietary name at the initial phase of the name review. Additionally, when applicable, at the same time DMEPA requests concurrence/non-concurrence with DDMAC's decision on the name. Any comments or concerns are addressed in the safety evaluator's assessment.

The Review Division is contacted a second time following our analysis of the proposed name. At this point, DMEPA conveys their decision to accept or reject the name. The regulatory division is requested to concur /not concur with DMEPA's final decision.

2.1.4 External Proprietary Name Risk Assessment

For this product, the Applicant submitted an external evaluation of the proposed proprietary name, Afresa. The Division of Medication Error Prevention and Analysis conducts an independent analysis and evaluation of the data provided, and responds to the overall findings of the assessment. When the external proprietary name risk assessment identifies potentially confusing names that were not captured in DMEPA's database searches or in the Expert Panel Discussion, these names are included in the Safety Evaluator's Risk Assessment and analyzed independently by the Safety Evaluator to determine if the potentially confusing name could lead to medication errors in usual practice settings.

After the Safety Evaluator has determined the overall risk assessment of the proposed name, the Safety Evaluator compares the findings of their overall risk assessment with the findings of the proprietary name risk assessment submitted by the Applicant. The Safety Evaluator then determines whether the Division's risk assessment concurs or differs with the findings.

2.1.5 Safety Evaluator Risk Assessment of the Proposed Proprietary Name

Based on the criteria set forth in Section 2.1, the Safety Evaluator Risk Assessment applies their individual expertise gained from evaluating medication errors reported to FDA to conduct a Failure Mode and Effects Analysis and provide an overall risk of name confusion. Failure Mode and Effects Analysis (FMEA) is a systematic tool for evaluating a process and identifying where and how it might fail.[6] When applying FMEA to assess the risk of a proposed proprietary name, DMEPA seeks to evaluate the potential for a proposed name to be confused with another drug name as a result of the name confusion and cause errors to occur in the medication use system. FMEA capitalizes on the predictable and preventable nature of medication errors associated with drug name confusion. FMEA allows the Agency to identify the potential for medication errors due to look- or sound-alike drug names prior to approval, where actions to overcome these issues are easier and more effective then remedies available in the post-approval phase.

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

In the initial stage of the Risk Assessment, the Safety Evaluator compares the proposed proprietary name to all of the names gathered from the above searches, expert panel evaluation, and studies, and identifies potential failure modes by asking: "Is the name Afresa convincingly similar to another drug name, which may cause practitioners to become confused at any point in the usual practice setting?" An affirmative answer indicates a failure mode and represents a potential for Afresa to be confused with another proprietary or established drug name because of look- or sound-alike similarity. If the answer to the question is no, the Safety Evaluator is not convinced that the names posses similarity that would cause confusion at any point in the medication use system and the name is eliminated from further review.

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

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

1. DDMAC finds the proposed proprietary name misleading from a promotional perspective, and the review Division concurs with DDMAC's findings. The Federal Food, Drug, and Cosmetic Act provides that labeling or advertising can misbrand a product if misleading representations are

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

made or suggested by statement, word, design, device, or any combination thereof, whether through a trade name or otherwise. [21 U.S.C 321(n); see also 21 U.S.C. 352(a) & (n)].

2. DMEPA identifies that the proposed proprietary name is misleading because of similarity in spelling or pronunciation to another proprietary or established name of a different drug or ingredient [CFR 201.10.(C)(5)].
3. FMEA identifies potential for confusion between the proposed proprietary name and other proprietary or established drug names, and demonstrates that medication errors are likely to result from the drug name confusion under the conditions of usual clinical practice.
4. The proposed proprietary name contains an USAN stem, particularly in a manner that is contradictory to the USAN Council's definition.
5. DMEPA staff identify a potential source of medication error within the proposed proprietary name. The proprietary name may be misleading, or inadvertently introduce ambiguity and confusion that leads to errors. Such errors may not necessarily involve confusion between the proposed drug and another drug product.

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 is awarded approval first has the right to the use the name, while DMEPA will recommend that the second product to reach approval seek an alternative name.

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

Furthermore, 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, can be identified and remedied prior to approval to avoid patient harm.

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

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

plausible strategies that could reduce the risk of medication error of the currently proposed name, and so DMEPA may be able to provide the Applicant with recommendations that reduce or eliminate the potential for error would render the proposed name acceptable.

3 RESULTS

3.1 PROPRIETARY NAME RISK ASSESSMENT

3.1.1 Database and Information Sources

The search of the internet, several standard published databases and information sources (see Section 7 References) yielded a total of 21 names as having some similarity to the name Afresa.

Sixteen of the 21 names were thought to look like Afresa. These include Afluria, Afrinol, Afrin, Atreza, Abreva, Cyclessa, Cipro XR, Apidra, Alesse, Aflexa, Akten, Alavert, Aptivus, (b) (4) (b) (4) and Alfenta. Two of the 21 names were thought to sound like Afresa. These include Apresazide and Aflaxen. The remaining three names were thought to look and sound similar to Afresa (Alvesco***, Natresa, and Iressa).

Additionally, we did not identify any United States Adopted Names (USAN) stems in the name, Afresa, as of March 10, 2009.

3.1.2 Expert Panel Discussion

The Expert Panel reviewed the pool of names identified by DMEPA staff (see section 3.1.1. above) and noted no additional names thought to have orthographic or phonetic similarity to Afresa. DDMAC had no concerns regarding the proposed name from a promotional perspective, and did not offer any additional comments relating to the proposed name.

3.1.3 FDA Prescription Analysis Studies

A total of 20 practitioners responded but none of the responses overlapped with any existing or proposed drug names. Six of the participants interpreted the name correctly as “Afresa,” with correct interpretation occurring in both the inpatient written studies (n=5) and the outpatient written studies (n=1). The remainder of the written responses misinterpreted the drug name as ‘Afrisa’ (n=8) or ‘Afrusa’ (n=1). In the verbal studies, all responses were misspelled phonetic variations of the proposed name, ‘Afrisa’ (n=5). See Appendix B for the complete listing of interpretations from the verbal and written prescription studies.

3.1.4 External Proprietary Name Risk Assessment

In the proposed name risk assessment submitted by the Applicant, (b) (4) identified and evaluated a total of 15 drug names thought to have some potential for confusion with the name Afresa. Five of the fifteen names were previously identified in our staff searches and include Alesse, Afrin, Apresoline, Iressa, and Abreva. Of the remaining ten names not previously identified by DMEPA, four of the names (Zyprexa, Arixtra, Atripla, and Celexa) were identified as having sound-alike similarity to Afresa, three names (Allegra, Lopressor, and Apri) were identified as having both look and sound-alike similarity to Afresa, while the remaining three names (Ativan, Antabuse, and Anusol) were identified as having look-alike similarity to Afresa.

3.1.5 Safety Evaluator Risk Assessment

Independent searches by the Safety Evaluator identified six additional names that were thought to look or sound similar to Afresa and represent a potential source of name confusion. The names are Aredia, Afrisal, Genesa, Canasa, (b) (4) and Apriso.

Therefore, a total of 37 names were analyzed to determine if the drug names could be confused with Afresa and represent a potential source of drug name confusion.

Failure mode and effect analysis was then applied to determine if the potential name, Afresa, could potentially be confused with any of the 37 names and lead to medication errors. This analysis determined that the name similarity between Afresa and the identified names was unlikely to result in medication errors with 36 of the 37 products identified for the reasons presented in Appendicies C-H.

The remaining product, Apidra, was determined to likely result in medication error due to the orthographic similarity of the proprietary names in addition to overlapping product characteristics to the proposed product (see Appendix H).

3.1.6 Comments from the Division of Metabolism and Endocrine Products (DMEP)

DMEP concurred with the assessment of the safety concerns and objection expressed by DMEPA in an email dated June 15, 2009. Additionally, DMEP did not have any other comments and/or clinical/other concerns on the proposed proprietary name.

4 DISCUSSION

4.1 PROPRIETARY NAME RISK ASSESSMENT

The results of the Proprietary Name Risk Assessment indicate that the proposed name, Afresa is vulnerable to name confusion that could lead to medication errors with Apidra.

4.1.1 Apidra

We have completed our review of this proposed proprietary name, Afresa, and have concluded that this name is unacceptable because the name is vulnerable to name confusion with the currently marketed product Apidra.

Orthographic similarities in conjunction with the product characteristic profiles between the products Apidra and Afresa increase the likelihood of medication errors in the usual practice setting between this name pair. Each name begins with the letter ‘A’, ends with the letter ’a’, has downstrokes in the same position of each name, and has a similar length. Additionally, both products share the same indication of use (short-acting insulins used for treatment in diabetes). Thus a pharmacist can dispense either product to a patient that is known to have diabetes and require insulin treatment. This is important because a pharmacist would likely not question a new prescription for one product if the patient has been receiving the other product, because they could conclude the patient is switching insulin regimens from one product to the other product. Thus a medication error is less likely to be detected by the pharmacist. We are particularly concerned with the potential for confusion between these two products because although they are both short-acting insulin products, they are not interchangeable. Administering a dose (in units) of one product when the dose was intended for the other product could result in serious harm to the patient as a result of an overdose or under dose of insulin.

Afresa
Apidra

As both Apidra and Afresa are insulin preparations, they can have overlapping numerical doses (in units) that can increase the potential for confusion. Afresa and Apidra will be administered as rapid acting insulin for diabetic patients to take just prior to meals. Both products will be used on a chronic and ongoing basis. Given the overwhelming similarity of the product characteristics, and similarity of this name pair when scripted, we do not recommend the use of Afresa.

5 CONCLUSIONS AND RECOMMENDATIONS

The Proprietary Name Risk Assessment findings indicate that the proposed name, Afresa, is vulnerable to name confusion with the currently marketed product Apidra which could lead to medication errors. As such, the Division of Medication Error Prevention objects to the use of the proprietary name, Afresa, for this product.

5.1 COMMENTS TO THE DIVISION

If you have further questions or need clarifications, please contact Mildred Wright, OSE Project Manager, at 301-796-1027.

5.2 COMMENTS TO THE APPLICANT

We have completed our review of this proposed proprietary name, Afresa, and have concluded that this name is unacceptable because the name is vulnerable to name confusion with the currently marketed product Apidra.

Orthographic similarities in conjunction with the similar product characteristic profiles between the products Apidra and Afresa increase the likelihood of medication errors in the usual practice setting between this name pair. The orthographic similarity of this name pair stems from the use of the same beginning and ending letter (a), same length, and downstrokes that appear in the same position of each name when scripted. Additionally, both products share the same indication of use (short-acting insulin used for treatment in diabetes), and can have overlapping numerical doses (in units) that can increase the potential for confusion. Afresa and Apidra will be administered as rapid acting insulin for diabetic patients to take just prior to meals and both products will be used on a chronic and ongoing basis. Thus a medication error is less likely to be detected by the pharmacist. We are particularly concerned with the potential for confusion between these two products because although they are both short-acting insulin products, they are not interchangeable. Administering a dose (in units) of one product when the dose was intended for the other product could result in serious harm to the patient as a result of an overdose or under dose of insulin. Given the overwhelming similarity of the product characteristics, and similarity of this name pair when scripted, we do not recommend the use of Afresa.

We note you have not submitted an alternate proprietary name for the proposed product. We recommend you submit an alternate name with a request for a proprietary name review.

6 REFERENCES

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

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

2. Phonetic and Orthographic Computer Analysis (POCA)

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

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

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

4. AMF Decision Support System [DSS]

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

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

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

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

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

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

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

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

Provides information regarding patent and trademarks.

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

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

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

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

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

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

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

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

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

List contains all the recognized USAN stems.

14. Red Book Pharmacy's Fundamental Reference

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

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

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

16. Medical Abbreviations Book

Contains commonly used medical abbreviations and their definitions.

APPENDICES

Appendix A:

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

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

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

Appendix B: **CDER Prescription Study Responses**

Inpatient Medication Order	Outpatient Medication Order	Voice Prescription
Afresa	Afresa	Afrisa
Afresa	Afrisa	Afrisa
Afresa	Afrisa	Afrisa
Afresa	Afrisa	Afrisa
Afresa	Afrisa	Afrisa
	Afrisa	
	Afrisa	
	Afrisa	
	Afusa	
	Afrisa	

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

Name	Name
Alavert	Anusol
(b) (4)	Apresazide
Akten	Zyprexa
Aptivus	Arixtra
(b) (4)	Atripla
Afrinol	Celexa
Cyclessa	Alvesco
Cipro XR	Alesse
Aflaxen	Allegra
(b) (4)	Lopressor
Ativan	Apri
Antabuse	

Appendix D: Product names that have not ever been marketed.

Proprietary Name	Similarity to Afresa	Status of product name
Natresa	Look and Sound	Natresa is registered in USPTO and other countries (SAEGIS) as unidentified "pharmaceutical preparations for the prevention and treatment of osteoporosis". Natresa does not appear to be currently marketed in the U.S. and cannot be found in commonly used databases.

Appendix E: Products withdrawn from the market and no generics are available.

Proprietary Name	Similarity to Afresa	
Genesa (arbutamine HCl)	Look and Sound	NDA # 20-420, withdrawn by commissioner on September 17, 2001.

Appendix F: Products marketed in foreign countries

Proprietary Name	Similarity to Afresa
Afrisal (unknown nasal preparation in Columbia)	Look

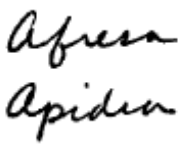
<u>Appendix G:</u> Single strength products with multiple differentiating product characteristics

Product name with potential for confusion	**Similarity to Afresa**	**Strength**	**Usual Dose (if applicable)**	**Differentiating Product Characteristics (Afresa vs. Product)**
Afresa	**N/A**	**15 units or 30 units**	**Given with meals (three times a day). Cartridge delivers 4 units (15 unit strength) or 8 units (30 unit strength) via** (b) (4) [redacted] **Patient may also be ordered concomitant long-acting subcutaneous insulin.**	**N/A**
Canasa **(mesalamine)**	Look and Sound	Rectal suppository: 1000 mg (30 count)	Insert one 1000 mg suppository in rectum daily at bedtime. Note: Suppositories should be retained for at least 1-3 hours to achieve maximum benefit. Note: Some patients may require rectal and oral mesalamine therapy concurrently.	Route of administration (rectal vs. inhalation); Frequency of administration (bedtime vs. at mealtime); Indication for use (GI disease vs. diabetes)
Aflexa **(glucosamine)** **nonprescription dietary supplement**	Look and Sound	Tablets: 340 mg	In clinical studies of arthritis, glucosamine dosage has typically been 1.5 g/day, as a single dose or in divided doses.	Route of administration (oral vs. inhalation) Indication (osteoarthritis vs. diabetes) Non-prescription vs. prescription status

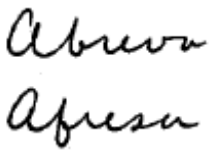
Product name with potential for confusion	**Similarity to Afresa**	**Strength**	**Usual Dose (if applicable)**	**Differentiating Product Characteristics (Afresa vs. Product)**
Afresa	**N/A**	**15 units or 30 units**	**Given with meals (three times a day). Cartridge delivers 4 units (15 unit strength) or 8 units (30 unit strength) via** (b) (4) **Patient may also be ordered concomitant long-acting subcutaneous insulin.**	**N/A**
Iressa (gefitinib) Note: In response to the lack of improved survival data from the ISEL trial, AstraZeneca has temporarily suspended promotion of this drug.	Look and Sound	Tablet: 250 mg	250 mg/day; consider 500 mg/day in patients receiving effective CYP3A4 inducers (e.g., rifampin, phenytoin)	Route of administration (oral vs. inhalation) Frequency of administration (once daily vs. three times daily with meals) Indication for use (oncology vs. diabetes)
Afluria (influenza virus vaccine)	Look	Injection, suspension: 5 mL (10 doses) or 0.5 mL (1 dose)	0.5 mL intramuscularly (1 dose per season)	Route of administration (intramuscular injection vs. inhalation) Frequency of administration (once per year vs. three times daily with meals) Indication for use (annual vaccination vs. diabetes)

Product name with potential for confusion	**Similarity to Afresa**	**Strength**	**Usual Dose (if applicable)**	**Differentiating Product Characteristics (Afresa vs. Product)**
Afresa	**N/A**	**15 units or 30 units**	**Given with meals (three times a day). Cartridge delivers 4 units (15 unit strength) or 8 units (30 unit strength) via** (b) (4) [redacted] **Patient may also be ordered concomitant long-acting subcutaneous insulin.**	**N/A**
Alfenta (alfentanil)	Look	Injection, solution: 500 mcg/mL (2 mL, 5 mL, 10 mL, 20 mL)	Doses should be titrated to appropriate effects; wide range of doses is dependent upon desired degree of analgesia/anesthesia Intravenous dose should be based on ideal body weight as per table in insert labeling (dose ranges from 8-245 mcg/kg for induction then 0.5-15 mcg/kg/min for maintenance during the procedure.	Route of administration (injection vs. inhalation) Frequency of administration (during procedure vs. three times daily with meals) Indication for use (anesthesia vs. diabetes) Area of use (under direct supervision of anesthestist vs. outpatient use)

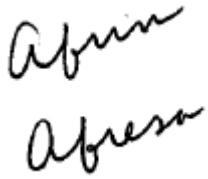
Appendix H: Potential confusing name

Afresa **(insulin inhalation powder)**	**15 units or 30 units**	**Given with meals (three times a day). Cartridge delivers 4 units (15 unit strength) or 8 units (30 unit strength) via** (b) (4) **Patient may also be ordered concomitant long-acting subcutaneous insulin.**
Failure Mode: **Name confusion**	**Causes** **(could be multiple)**	**Effects**
Apidra **Apidra OptiClik** **(insulin glulisine)** Apidra: 100 units/mL (10 mL) Apidra OptiClik: 100 units/mL (15 mL)	Orthographic similarity: ('Ap-' vs. 'Af-') may appear similar when scripted; similar endings ('-ra' vs. '-sa')  Products share indications and patient populations; both are insulins and used for treatment in diabetes. Overlapping or identical doses: both products are dosed in units of insulin	Orthographic similarities in the names increase the likelihood of medication errors in the usual practice setting. The letter 'p' in Apidra and the letter 'f' in Afresa create a downstroke in the same position of each name although the letter 'd' in Apidra can help to differentiate the names. Apidra is a different dosage form (insulin glulisine for injection) than Afresa (insulin powder for inhalation) with a different route of delivery. However, both Apidra and Afresa share indications and patient populations; both are insulins and used for treatment in diabetes. Thus a pharmacist can dispense either product to a patient that is known to have diabetes and require insulin treatment. As both Apidra and Afresa are insulin preparations, they will have overlapping numerical doses (in units) that can increase the potential for confusion. Both will be administered as rapid acting insulin for diabetic patients to take just prior to meals. Both products will be used on a chronic and ongoing basis. The orthographic differences are not adequate to differentiate the products. Additionally, the product characteristics, as mentioned above, have numerous overlaps that increase the similarities between products making it difficult to reliably distinguish between this name pair. We are particularly concerned with the potential for confusion between these two products because although they are both insulin products, they are not interchangeable. Administering a dose (in units) of one product when the dose was intended for the other product could result in serious harm to the patient.
Aredia **(pamidronate)**	Orthographic similarity: both names start with the letter 'A' and have similar endings ('-ra' vs. '-ia')	Orthographic differences in the names minimize the likelihood of medication errors in the usual practice setting. Specifically, an upstroke from the letter 'd' in Aredia and the downstroke from the letter 'f' in Afresa standout and help to differentiate the names.

Injection, powder for reconstitution: 30 mg, 90 mg Injection, solution: 3 mg/mL (10 mL); 6 mg/mL (10 mL); 9 mg/mL (10 mL) 60-90 mg, as a single dose over 2-24 hours, repeated after 2-3 weeks or up to 2-3 months as needed. Paget's Disease: 30 mg intravenously over 4 hours daily for 3 consecutive days	Aredia Afresa Numerical overlap in strength or dose (30 mg vs. 30 units)	*Rationale:* Aredia is a different dosage form (injection vs. powder for inhalation) than Afresa with a different route of delivery. Aredia is administered as a single dose of 30 mg, which may be repeated daily for 3 consecutive days; whereas Afresa will be administered three times a day just prior to meals on an ongoing basis as part of insulin therapy. Thus the two products have different dosage frequencies and length of treatment regimens. Although the two products have a numerical overlap in strength or dose (30 mg vs. 30 units), the unit of measure between the two products does differ and may help differentiate them when included on a prescription. Aredia will be ordered, prepared, and administered to the patient in an institutional or clinical setting. Aredia will be administered via infusion to the patient by a health care professional familiar with its use, and is not available in retail pharmacies. In contrast, Afresa will most likely be administered on an outpatient and continuing basis by the patient. Although Afresa may be used by hospitalized patients, it is not likely that these two products would be confused due to the different dosage forms, route of delivery, setting of use, and indications. Thus due to orthographic differences, as well as differences in the dosage formulation and route of delivery, DMEPA believes it is unlikely that a medication error will occur.
Atreza **(atropine sulfate)** Tablets: 0.4 mg Pre-operative use: 2 mg orally 30-60 min prior to anesthesia GI disorders: 0.3-1.2 mg orally every 4 to 6 hours **Atreza brand is no longer marketed although generics are available**	Orthographic similarity: ('At-' vs. 'Af-') may appear similar when scripted; similar endings ('-za' vs. '-sa') Afresa Atreza Phonetic similarity: Both names begin with an 'A', and they can share a similar phonetic ending '-suh'. The names can be pronunced similarly (a-tres-suh vs. a-fres-uh) when spoken.	Orthographic differences in the names minimize the likelihood of medication errors in the usual practice setting. Specifically, the letter 'z' in Atreza contibutes a downstroke when scripted and helps to differentiate the names. *Rationale:* Atreza is a different dosage form (tablet) than Afresa (powder for inhalation). Atreza also has a different route of delivery (oral ingestion) than Afresa (oral inhalation). Both products are administered several times a day, with Atreza given pre-operatively or every 4 to 6 hours, and Afresa administered three times a day with meals. Atreza is available in a single strength, so the strength (0.4 mg) may be omitted on a prescription, however, the prescription will contain additional information that can help differentiate an Atreza prescription, such as number of tablets, the mg dose ordered, or a dosing frequency in hours.

		Additionally, Atreza is a discontinued brand of atropine sulfate tablets. Although most prescribers order atropine by the established name rather than a brand name, even if a prescriber specifies the Atreza product and omits the strength, the prescriber will be including the ordered dose in terms of number of tablets or milligrams along with a frequency of use that will differentiate between a prescription for Atreza and Afresa. Thus due to orthographic differences, as well as differences in the dosage formulation, route of delivery, and any other instructions for use, DMEPA believes it is unlikely that a medication error will occur.
Abreva **(docusanol)** **non-prescription** Cream, topical: 10% (2 g) Apply 5 times/day to affected area of face or lips. Start at first sign of cold sore or fever blister and continue until healed.	Orthographic similarity: (‘Ab-‘ vs. ‘Af-‘) may appear similar when scripted; similar endings (‘-va’ vs. ‘-sa’) 	Orthographic differences in the names minimize the likelihood of medication errors in the usual practice setting. Although the letter ‘b’ in Abreva and the letter ‘f’ in Afresa can look similar when scripted, the diffences between the letter ‘v’ in Abreva and the letter ‘s’ in Afresa can help to differentiate the names. *Rationale:* Abreva is a different dosage form (topical cream) than Afresa (insulin powder for inhalation) with a different route of delivery. Abreva is applied five times a day on an intermittent basis when a cold sore appears until it heals. Afresa will be used on an ongoing basis, three times a day before meals to treat a chronic disease (diabetes). Abreva is available in a single strength (10%) and is a non-prescription product. Thus an order for Abreva that lacks a strength, such as “Abreva, dispense 1” could be seen. However, there may be additional directions for use on a Abreva prescription such as “apply to sores until healed.” Prescriptions for Afresa wil contain a dose in units of insulin or number of cartridges. There are also likely to be additional directions for use on an Afresa prescription, such as “use three times a day before meals’ or something similar. This additional information on prescriptions for Abreva/Afresa will decrease the potential for confusion between the two names. Patients ordered Afresa will need individual training on the proper preparation and administration of the product. In the unlikely event that an order for Abreva/Afresa is misinterpreted and the patient gets the wrong product, the patient will recognize the error due to the product differences and packaging from what they were expecting: the Afresa inhaler/cartridges versus the Abreva tube.

		Thus, due to orthographic differences, as well as differences in the dosage formulation, directions for use, and route of delivery, DMEPA believes it is unlikely that a medication error will occur.
Apriso **(mesalamine)** Look Capsule, delayed and extended release: 0.375 g 1.5 g (4 capsules) orally once daily in the morning	Orthographic similarity: ('Ap-' vs. 'Af-') may appear similar when scripted; similar endings ('-so' vs. '-sa')  Overlapping numerical dose: the Apriso dose may be ordered as 4 capsules and the Afresa 15 unit cartridge delivers 4 units of insulin. Thus the Afresa dose could be ordered as 4 units on a prescription.	Orthographic differences in the names minimize the likelihood of medication errors in the usual practice setting. Specifically, the letter 'p' in Apriso is noticeable when scripted and the letter 'I' (when dotted) helps to differentiate the names. *Rationale:* Apriso is a different dosage form (capsule) than Afresa (powder for inhalation). Apriso also has a different route of delivery (oral ingestion) than Afresa (oral inhalation). Apriso is administered once daily in the morning, whereas Afresa is administered three times a day with meals. Apriso is available in a single strength, so the strength (0.375 mg) may be omitted on a prescription, however, the prescription would need to contain a dose (e.g., 1.5 g) or number of capsules (e.g., 4) to be dispensed. A prescription for Afresa would contain the dose in units of insulin or number of cartridges. Although there is an overlap with the number 4, although there should be accompanying units of measure (capsules for Apriso and units or number of cartridges for Afresa) on the prescription, as well as additional instructions for use (e.g., three times a day before meals), that may help differentiate the names. The two products and their packaging look very different. Apriso will be dispensed in a prescription vial or bottle containing capsules, whereas Afresa will be marketed as unit-dose cartridges with or without an inhaler. Patients prescribed Afresa will need individual training on the proper preparation and administration of Afresa. In the unlikely event that an order for Afresa/Apriso is misinterpreted and the patient gets the wrong product, the patient will recognize the error due to product differences and packaging from what they were expecting: the Afresa inhaler/cartridges vs. Apriso capsules. Thus due to orthographic differences, as well as differences in the dosage formulation, route of delivery, and any other instructions for use, DMEPA believes it is unlikely that a medication error will occur with this name pair.
Afrin **(oxymetazoline HCl)**	Orthographic similarity: Identical prefix when scripted ('Afri-' vs.	Orthographic differences in the names minimize the likelihood of medication errors in the usual practice setting. Specifically, the letter 'n' in AFrion as compared

Non-prescription Solution, intranasal, as hydrochloride [spray]: 0.05% (15 mL, 30 mL) Afrin® Extra Moisturizing: 0.05% (15 mL) Afrin® Original: 0.05% (15 mL, 30 mL) Afrin® Severe Congestion: 0.05% (15 mL) Afrin® Sinus: 0.05% (15 mL) Instill 2-3 sprays into each nostril twice daily	'Afre-')  Identical route of administration (inhalation): although Afresa is administered via the mouth and Afrin is administered via the nose. Overlapping numerical dose: Afresa requires 2 inhalations to obtain the entire contents of the cartridge and the Afrin dose can be 2 sprays.	to the suffix '-sa' in AFresa will differentiate between the two names. *Rationale:* Afrin is a different dosage form (intranasal solution) than Afresa (powder for inhalation), and both products are inhaled, however Afrin is administered via the nose and Afresa is administered via the mouth. Both products may be ordered in terms of 2 puffs or inhalations, although Afrin is administered twice daily and Afresa administered three times a day with meals. Afrin is available in a single strength (0.05%) and is a non-prescription product, although there are several different Afrin brand name modifiers (e.g., Severe Congestion, Sinus, etc.) that are used. Often, Afrin is identified without the modifier. Thus an order for "Afrin, dispense 1" is commonly seen. Whereas an order for Afresa would need to specify the strength of cartridge or a unit dose in terms of units of insulin (4, 8, 15, or 30 units), or as the number of cartridges. If Afresa is ordered in terms of 'puffs' or 'inhalations' the order would need to be clarified to determine the strength of Afresa to dispense. This additional information on a prescription for Afresa will differentiate it from an order for Afrin. The two products and their packages look very different. Afrin is marketed in a nasal spray bottle or aspirator, whereas Afresa will be marketed in unit-dose cartridges with or without an inhaler. Patients prescribed AFresa will need individual training on the proper preparation and administration of their prescribed product. In the unlikely event that an order for Afresa/Afrin is misinterpreted and the patient gets the wrong product, the patient will recognize the error due to the product differences and packaging from what they were expecting: the Afresa inhaler/cartridges versus the Afrin nasal spray. Thus due to orthographic differences, as well as differences in the dosage formulation, packaging, route of delivery, and any other instructions for use, DMEPA believes it is unlikely that a medication error will occur.

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

/s/

Laura Pincock
6/30/2009 12:53:19 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
6/30/2009 12:55:07 PM
DRUG SAFETY OFFICE REVIEWER