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APPLICATION NUMBER:

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PROPRIETARY NAME REVIEW(S)

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

Proprietary Name Review

Date: August 3, 2012

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Drug Name and Strength: Bethkis (Tobramycin) Inhalation Solution
300 mg/4 mL

Application Type/Number: NDA 201820

Submission Number: 0037

Applicant/Sponsor: Chiesi Pharmaceuticals Inc.

OSE RCM #: 2012-1152

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

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1 INTRODUCTION

This review evaluates the proposed proprietary name, Bethkis, 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

1.2 PRODUCT INFORMATION

The following product information is provided in the May 7, 2012 proprietary name submission.

- Active Ingredient: Tobramycin
- Indication of Use: management of cystic fibrosis patients with *P. aeruginosa*
- Route of Administration: Oral inhalation via nebulizer
- Dosage Form: Solution for oral inhalation
- Strength: 300 mg/4 mL
- Dose and Frequency: 300 mg twice daily
- How Supplied: Each carton contains a 28 day supply of 4 mL single use ampoules.
- Storage: Room temperature or Refrigerated

2 RESULTS

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

2.1 PROMOTIONAL ASSESSMENT

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

2.2 SAFETY ASSESSMENT

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

2.2.1 United States Adopted Names (USAN) SEARCH

The May 16, 2012 search of the United States Adopted Name (USAN) stems did not identify that a USAN stem is present in the proposed proprietary name.

2.2.2 Components of the Proposed Proprietary Name

The Applicant indicated in their submission that the proposed name, Bethkis, is derived from two words: Beth (woman’s name) and Kiss. This name composition 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

Thirty-three practitioners participated in DMEPA’s prescription studies. The interpretations did not overlap with or appear or sound similar to any currently marketed products. Most of the written prescriptions were interpreted correctly (13 of 15 inpatient orders and 8 of 9 outpatient orders) and the key error in the voice orders included confusion of the ‘b’ for a ‘v’ which was expected. See Appendix C for the complete listing of interpretations from the verbal and written prescription studies.

2.2.4 Comments from Other Review Disciplines

In response to the OSE, May 24, 2012 e-mail, the Division of Anti-Infective Products (DAIP) did not forward any comments or concerns relating to the proposed name at the initial phase of the proprietary name review.

2.2.5 Failure Mode and Effects Analysis of Similar Names

Appendix B lists possible orthographic and phonetic misinterpretations of the letters appearing in the proposed proprietary name, Bethkis. Table 1 lists the names with orthographic, phonetic, or spelling similarity to the proposed proprietary name, Bethkis identified by the primary reviewer, the Expert Panel Discussion (EPD), and other review disciplines. Table 1 also includes the names identified from the FDA Prescription simulation.

Table 1: Collective List of Potentially Similar Names (DMEPA, EPD, Other Disciplines, FDA Name Simulation Studies, and External Name Study if applicable)

Look Similar					
<i>Name</i>	<i>Source</i>	<i>Name</i>	<i>Source</i>	<i>Name</i>	<i>Source</i>
Brethine	EPD	Bulk-K	EPD	Baclofen	EPD
BeFlex	EPD	Beta-HC	EPD	Bicillin	EPD
Betatrex	EPD	Betalin	EPD	Betadine	EPD
Butalan	EPD	Butrans	EPD	Biltricide	EPD
Butibel	EPD	Betanis***	EPD	Betatar	EPD
Butalix	EPD	Bebulin	EPD	Bel-Tabs	EPD
Beldin	EPD	Belladol	EPD	Bellatal	EPD
Bidhist	EPD				

Our analysis of the 22 names contained in Table 1 considered the information obtained in the previous sections along with their product characteristics. We determined all 22 names will not pose a risk for confusion as described in Appendix D through E.

2.2.6 Communication of DMEPA's Final Decision to Other Disciplines

DMEPA communicated our findings to the Division of Anti-Infective Products via e-mail on July 10, 2012. At that time we also requested additional information or concerns that could inform our review. Per e-mail correspondence from the Division of Anti-Infective Products on July 16, 2012, they stated no additional concerns with the proposed proprietary name, Bethkis.

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 Brantley Dorch, OSE project manager, at 301-796-0150

3.1 COMMENTS TO THE APPLICANT

We have completed our review of the proposed proprietary name, Bethkis, and have concluded that this name is acceptable. However, if any of the proposed product characteristics as stated in your May 7, 2012 submission are altered, DMEPA rescinds this finding and the name must be resubmitted for review.

Additionally, the proposed proprietary name must be re-reviewed 90 days prior to approval of the NDA. The conclusions upon re-review are subject to change.

4 REFERENCES

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

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

2. Phonetic and Orthographic Computer Analysis (POCA)

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

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

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

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

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

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

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

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

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

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

USPTO provides information regarding patent and trademarks.

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

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

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

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

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

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

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

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

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

USAN Stems List contains all the recognized USAN stems.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

APPENDICES

Appendix A

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

The safety assessment is conducted by DMEPA. DMEPA staff search a standard set of databases and information sources to identify names that are similar in pronunciation, spelling, and orthographically similar when scripted to the proposed proprietary name. Additionally, we consider inclusion of USAN stems or other characteristics that when incorporated into a proprietary name may cause or contribute to medication errors (i.e., dosing interval, dosage form/route of administration, medical or product name abbreviations, names that include or suggest the composition of the drug product, etc.). DMEPA defines a medication error as any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer.¹

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

The DMEPA primary reviewer assigned to evaluate the proposed proprietary name is responsible for considering the collective findings, and provides an overall risk assessment of the proposed proprietary name. DMEPA bases the overall risk assessment on the findings of a Failure Mode and Effects Analysis (FMEA) of the proprietary name and misleading nature of the proposed proprietary name with a focus on the avoidance of medication errors.

DMEPA uses the clinical expertise of its staff to anticipate the conditions of the clinical setting where the product is likely to be used based on the characteristics of the proposed product. DMEPA considers the product characteristics associated with the proposed product throughout the risk assessment because the product characteristics of the

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

proposed may provide a context for communication of the drug name and ultimately determine the use of the product in the *usual* clinical practice setting.

Typical product characteristics considered when identifying drug names that could potentially be confused with the proposed proprietary name include, but are not limited to; established name of the proposed product, proposed indication of use, dosage form, route of administration, strength, unit of measure, dosage units, recommended dose, typical quantity or volume, frequency of administration, product packaging, storage conditions, patient population, and prescriber population. 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		
	<i>Potential Causes of Drug Name Similarity</i>	<i>Attributes Examined to Identify Similar Drug Names</i>	<i>Potential Effects</i>
Look-alike	Similar spelling	Identical prefix Identical infix Identical suffix Length of the name Overlapping product characteristics	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> 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 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 possess similarity that would cause confusion at any point in the medication use system, thus the name is eliminated from further review.

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

“Could the confusion of the drug names conceivably result in medication errors in the usual practice setting?”

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

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

- a. OPDP finds the proposed proprietary name misleading from a promotional perspective, and the Review Division concurs with OPDP’s findings. The Federal Food, Drug, and Cosmetic Act provides that labeling or advertising can misbrand a product if misleading representations are made or suggested by statement, word, design, device, or any combination thereof, whether through a PROPRIETARY name or otherwise [21 U.S.C 321(n); See also 21 U.S.C. 352(a) & (n)].
- b. DMEPA identifies that the proposed proprietary name is misleading because of similarity in spelling or pronunciation to another proprietary or established name of a different drug or ingredient [CFR 201.10.(C)(5)].

- c. FMEA identifies the potential for confusion between the proposed proprietary name and other proprietary or established drug name(s), and demonstrates that medication errors are likely to result from the drug name confusion under the conditions of usual clinical practice.
- d. The proposed proprietary name contains an USAN (United States Adopted Names) stem.
- e. DMEPA identifies a potential source of medication error within the proposed proprietary name. For example, the proprietary name may be misleading or, inadvertently, introduce ambiguity and confusion that leads to errors. Such errors may not necessarily involve confusion between the proposed drug and another drug product but involve a naming characteristic that when incorporated into a proprietary name, may be confusing, misleading, cause or contribute to medication errors.

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

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

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

Furthermore, post-marketing experience has demonstrated that medication errors resulting from drug name confusion are notoriously difficult to rectify post-approval. Educational and other post-approval efforts are low-leverage strategies that have had limited effectiveness at alleviating medication errors involving drug name confusion. Sponsors have undertaken higher-leverage strategies, such as drug name changes, in the

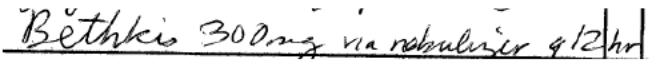
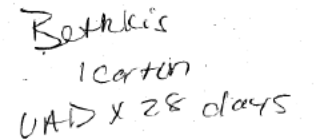
past but at great financial cost to the Sponsor and at the expense of the public welfare, not to mention the Agency’s credibility as the authority responsible for approving the error-prone proprietary name. Moreover, even after Sponsors’ have changed a product’s proprietary name in the post-approval phase, it is difficult to eradicate the original proprietary name from practitioners’ vocabulary, and as a result, the Agency has continued to receive reports of drug name confusion long after a name change in some instances. Therefore, DMEPA believes that post-approval efforts at reducing name confusion errors should be reserved for those cases in which the potential for name confusion could not be predicted prior to approval.

Appendix B: Letters with Possible Orthographic or Phonetic Misinterpretation

Letters in Name, Glatopa	Scripted may appear as	Spoken may be interpreted as
Upper case ‘B’	‘R’	‘P’, ‘D’, ‘V’
Lower case ‘b’	‘l’, ‘h’, ‘k’	‘P’, ‘D’, ‘V’
Lower case ‘e’	‘a’, ‘i’, ‘l’, ‘p’	Any vowel
Lower case ‘t’	‘r’, ‘f’, ‘x’, ‘d’	‘D’
Lower case ‘h’	‘k’, ‘b’, ‘n’, ‘L’	-
Lower case ‘k’	‘x’, ‘h’, ‘la’	‘C’, ‘G’
Lower case ‘i’	‘e’	Any vowel
Lower case ‘s’	‘G’, ‘5’, ‘g’, ‘n’	‘X’

Appendix C: Prescription Simulation Samples and Results

Figure 1. Bethkis Study (Conducted on May 25, 2012)

Handwritten Requisition Medication Order	Verbal Prescription
<p><u>Medication Order:</u> </p> <p><u>Outpatient Prescription:</u> </p>	<p>Bethkis UAD Dispense #1</p>

FDA Prescription Simulation Responses (Aggregate 1 Rx Studies Report)

84 People Received Study
33 People Responded

Study Name: Bethkis

Total	15	9	9	
INTERPRETATION	INPATIENT	VOICE	OUTPATIENT	TOTAL
BESKISS	0	2	0	2
BETHKIS	13	3	8	24
BETHLEIS	1	0	0	1
BETHSEIS	1	0	0	1
BETTKIS	0	0	1	1
VESKEN	0	1	0	1
VES-KIT	0	1	0	1
VESKITS ??	0	1	0	1
VETHKISS	0	1	0	1

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

Proprietary Name	Active Ingredient	Similarity to Bethkis	Failure preventions
Lioresal	Baclofen	Look alike for established name	The pair has sufficient orthographic differences.
Beta-HC	Hydrocortisone	Look alike	The pair has sufficient orthographic differences.
Bicillin	Penicillin G Benzathine	Look alike	The pair has sufficient orthographic differences.

Proprietary Name	Active Ingredient	Similarity to Bethkis	Failure preventions
Betatrex	Betamethasone Valerate	Look alike	The pair has sufficient orthographic differences.
Betalin	Cyanocobalamin established name for Betalin 12 Thiamine HCL established name for Betalin S Pyridoxine HCL established name for Hexa-Betalin	Look alike	The pairs have sufficient orthographic differences. The name Betalin was identified as a look alike without the modifier however the approved names include 3 different modifiers. The name Betalin without any modifiers is not an approved proprietary name.
Betadine	Povidone-Iodine	Look alike	The pair has sufficient orthographic differences.
Butalan	Butabarbital	Look alike	The pair has sufficient orthographic differences.
Butrans	Buprenorphine	Look alike	The pair has sufficient orthographic differences.
Biltricide	Praziquantel	Look alike	The pair has sufficient orthographic differences.
Butibel	Belladonna alkaloids / Butabarbital	Look alike	The pair has sufficient orthographic differences.
Betanis***	Mirabegron	Look alike	The pair has sufficient orthographic differences. Identified in proposed names database. Betanis was denied by DMEPA due to orthographic and phonetic similarities with Protonix. The established name for NDA 202611 is approved and marketed under the proprietary name, Myrbetriq.
Betatar	Coal tar	Look alike	The pair has sufficient orthographic differences.

Proprietary Name	Active Ingredient	Similarity to Bethkis	Failure preventions
Butalix	unknown	Look alike	Unable to find product characteristics in commonly used drug databases. The pair has sufficient orthographic differences.
Bebulin	Factor IX human complex	Look alike	The pair has sufficient orthographic differences.
Beldin	Diphenhydramine	Look alike	The pair has sufficient orthographic differences.
Belladol	Homeopathic substance	Look alike	The pair has sufficient orthographic differences.
Bellatal	Atropine /hyoscyamine /phenobartital /scopolamine hydrobromide	Look alike	The pair has sufficient orthographic differences.
Bidhist	Brompheniramine maleate	Look alike	The pair has sufficient orthographic 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.

<p>Proposed name: Bethkis</p> <p>Dosage Form(s): Solution for oral inhalation</p> <p>Strength(s): 300 mg/ 4 mL</p> <p>Usual Dose and Frequency and Route: 300 mg twice daily inhaled via nebulizer for 28 days</p>	<p>Failure Mode: Incorrect Product Ordered/ Selected/Dispensed or Administered because of Name confusion</p> <p>Causes (could be multiple)</p>	<p>Prevention of Failure Mode</p> <p>In the conditions outlined below, the following combination of factors, are expected to minimize the risk of confusion between these two names</p>
<p>Brethine (Terbutaline Sulfate)</p> <p><u>Strength and Dosage Form:</u> 1 mg/ mL injectable, 2.5 mg and 5 mg tablets</p> <p><u>Dose, Route and Frequency:</u> 2.5 mg to 5 mg orally every 6 hours (up to 15 mg per day) OR 0.25 mg subcutaneously, may repeat in 15 to 30 minutes (maximum 0.5 mg per 4 hour period)</p>	<p>Orthographic similarity to both the established and proprietary names</p> <p>Both names start with the same letter ‘B’. When scripted the letter string Breth- may look like the string Beth-.</p> <p>Overlapping product characteristics</p> <p>Brethine injection and Bethkis are single strength.</p>	<p>Orthographic differences</p> <p>Bethkis has an additional upstroke ‘k’ vs. Brethine, making the shapes of each name sufficiently different when scripted.</p> <p>Key differences in product characteristics</p> <p><u>Strength:</u></p> <p>Brethine oral tables have 2 strengths and must be written on a prescription vs. Bethkis which is single strength. There is no overlap in strength.</p> <p><u>Frequency:</u></p> <p>Brethine injection is given once with a possible repeat vs. the scheduled twice daily administration with Bethkis.</p> <p><u>Route of Administration:</u></p> <p>Brethine is available as oral tablets and an injectable. Therefore, the route of administration for Brethine must be specified on the order and is a differentiating characteristic from the inhaled route of administration for Bethkis.</p>

<p>Proposed name: Bethkis</p> <p>Dosage Form(s): Solution for oral inhalation</p> <p>Strength(s): 300 mg/ 4 mL</p> <p>Usual Dose and Frequency and Route: 300 mg twice daily inhaled via nebulizer for 28 days</p>	<p>Failure Mode: Incorrect Product Ordered/ Selected/Dispensed or Administered because of Name confusion</p> <p>Causes (could be multiple)</p>	<p>Prevention of Failure Mode</p> <p>In the conditions outlined below, the following combination of factors, are expected to minimize the risk of confusion between these two names</p>
<p>Bulk-K (Psyllium)</p> <p><u>Strength and Dosage Form:</u> 3.4 g / dose powder for suspension (available in 392 g package)</p> <p><u>Dose, Route and Frequency:</u> Based on general Psyllium information: 1.25 g to 30 g per day orally in divided doses. Unknown if there is a dosing device (e.g. scoop etc.) potentially the dose may be one or multiple scoops.</p>	<p>Orthographic similarity</p> <p>Both names start with the same letter ‘B’ and both have three upstrokes in the same positions.</p> <p>Overlapping product characteristics</p> <p>Frequency may overlap (twice daily), and both are single strength products. If a dosing device is present the dose may be similar (e.g. 1 scoop vs. 1 neb)</p>	<p>Orthographic differences</p> <p>Bulk-K appears shorter than Bethkis (5 letters vs. 7), and Bethkis has a cross-stroke ‘t’ vs. no cross-stroke in Bulk-K making the names appear sufficiently different.</p>

<p>Proposed name: Bethkis</p> <p>Dosage Form(s): Solution for oral inhalation</p> <p>Strength(s): 300 mg/ 4 mL</p> <p>Usual Dose and Frequency and Route: 300 mg twice daily inhaled via nebulizer for 28 days</p>	<p>Failure Mode: Incorrect Product Ordered/ Selected/Dispensed or Administered because of Name confusion</p> <p>Causes (could be multiple)</p>	<p>Prevention of Failure Mode</p> <p>In the conditions outlined below, the following combination of factors, are expected to minimize the risk of confusion between these two names</p>
<p>BeFlex (acetaminophen / phenyltoloxamine citrate)</p> <p><u>Strength and Dosage Form:</u> 500 mg / 55 mg tablet</p> <p><u>Dose, Route and Frequency:</u></p> <p>0.5 to 1 tablet orally every 4 hours (up to 5 tablets per day) as needed for minor pain. Information based on ZFlex which has the same active ingredients and strength.</p>	<p>Orthographic similarity</p> <p>Both names start with the same letter ‘B’ and both have two upstrokes in the same positions ‘fl’ vs. ‘th’.</p> <p>Overlapping product characteristics</p> <p>Similarity in dose (1 tab vs. 1 neb)</p>	<p>Orthographic differences</p> <p>Bethkis has an additional upstroke ‘k’ vs. BeFlex, making the shapes of each name sufficiently different when scripted.</p> <p>Key differences in product characteristics</p> <p><u>Frequency:</u></p> <p>BeFlex is given frequently-every 4 hours as needed vs. twice daily administration of Bethkis.</p>

<p>Proposed name: Bethkis</p> <p>Dosage Form(s): Solution for oral inhalation</p> <p>Strength(s): 300 mg/ 4 mL</p> <p>Usual Dose and Frequency and Route: 300 mg twice daily inhaled via nebulizer for 28 days</p>	<p>Failure Mode: Incorrect Product Ordered/ Selected/Dispensed or Administered because of Name confusion</p> <p>Causes (could be multiple)</p>	<p>Prevention of Failure Mode</p> <p>In the conditions outlined below, the following combination of factors, are expected to minimize the risk of confusion between these two names</p>
<p>Bel-Tabs (Belladonna alkaloids / Ergotamine tartrate / Phenobarbital)</p> <p><u>Strength and Dosage Form:</u> 0.2 mg / 0.6 mg / 40 mg</p> <p><u>Dose, Route and Frequency:</u> 1 tablet orally twice daily.</p>	<p>Orthographic similarity</p> <p>Both names start with the same letter ‘B’ and have the same number of letters (n=7). Both names have the same number of upstrokes.</p> <p>Overlapping product characteristics</p> <p>Similarity in dose, (1 tab vs. 1 neb), single strength products. Overlapping frequency of administration (twice daily).</p>	<p>Orthographic differences</p> <p>The last upstrokes, ‘b’ in Bel-Tabs and ‘k’ in Bethkis, are in different positions. The ‘a’ in Bel-Tabs separates the three upstrokes, giving it a different appearance in shape from Bethkis when scripted, which contains three consecutive upstrokes.</p> <p>Key differences in product characteristics</p> <p><u>Availability:</u> Action has been taken by the FDA via issuing warning letters to manufacturers of ergotamine containing products to cease the production and marketing of these unapproved drugs. The exception is a group of five marketed, approved versions of ergotamine-containing products (Cafergot, DHE 45, Ergomar, Migergot and Migranal). FDA news release P07-33 March 1, 2007. None of the approved ergotamine-containing products contain all of the active ingredients in Bel-Tabs.</p>

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/s/

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