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RESEARCH**

APPLICATION NUMBER:

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PROPRIETARY NAME REVIEW(S)

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

Proprietary Name Review

Date: September 13, 2013

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Drug Name and Strength: Nexium 24HR (Esomeprazole) Delayed-release
Capsules, 20 mg

Application Type/Number: NDA 204655

Submission Number: 5

Applicant: AstraZeneca

OSE RCM #: 2013-1565

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1 INTRODUCTION

This review evaluates the proposed proprietary name, Nexium 24HR, from a safety and promotional perspective.

The Applicant currently markets Nexium (Esomeprazole Magnesium) Delayed-Release Capsules, 20 mg and 40 mg, as prescription (Rx) products. On May 30, 2013, the Applicant filed NDA 204655 seeking over-the-counter (OTC) marketing approval for the 20 mg strength under the proposed new indication heartburn. The Applicant also plans to continue to market the 20 mg strength for Rx indications if OTC marketing is approved.

The sources and methods used to evaluate the proposed name are outlined in the reference section and Appendix A, respectively.

1.1 REGULATORY HISTORY

Nexium (Esomeprazole Magnesium) Delayed-Release Capsules, 20 mg and 40 mg, were approved as prescription drug products on February 20, 2001 (NDA 021153). In addition to the capsules formulation, Nexium Delayed-release Suspension, dosage packets containing 2.5 mg, 5 mg, 10 mg, 20 mg and 40 mg, was approved as a prescription product on October 20, 2006 (NDA 021957). Nexium IV (Esomeprazole Sodium) Injection, 20 mg and 40 mg per vial, were approved on March 31, 2005 (NDA 021689).

DMEPA previously found the proposed proprietary name, Nexium 24HR, acceptable under IND 111185 in OSE RCM# 2012-2516 dated April 17, 2013.

1.2 PRODUCT INFORMATION

The following product information is provided in the July 10, 2013 proprietary name submission.

<p>Drug Facts</p> <p>Active ingredient (in each capsule) Purpose</p> <p>Esomeprazole magnesium 22.3 mg Acid reducer (equivalent to esomeprazole 20 mg)</p>	<p>Drug Facts (continued)</p> <p>if pregnant or breast-feeding, ask a health professional before use. Keep out of reach of children. In case of overdose, get medical help or contact a Poison Control Center right away.</p>
<p>Uses</p> <ul style="list-style-type: none"> ■ treats frequent heartburn (occurs 2 or more days a week) ■ not intended for immediate relief of heartburn; this drug may take 1 to 4 days for full effect 	<p>Directions</p> <ul style="list-style-type: none"> ■ adults 18 years of age and older ■ this product is to be used once a day (every 24 hours), every day for 14 days ■ it may take 1 to 4 days for full effect (b) (4) <p>14-Day Course of Treatment</p> <ul style="list-style-type: none"> ■ swallow 1 capsule with a glass of water before eating in the morning ■ take every day for 14 days ■ do not take more than 1 capsule a day ■ swallow whole. Do not crush or chew capsules. ■ do not use for more than 14 days unless directed by your doctor <p>Repeated 14-Day Courses (if needed)</p> <ul style="list-style-type: none"> ■ you may repeat a 14-day course every 4 months ■ do not take for more than 14 days or more often than every 4 months unless directed by a doctor <p>■ children under 18 years of age: ask a doctor before use. Heartburn in children may sometimes be caused by a serious condition.</p>
<p>Warnings</p> <p>Allergy alert: Do not use if you are allergic to esomeprazole (b) (4)</p>	<p>Other Information</p> <ul style="list-style-type: none"> ■ read the directions and warnings before use ■ keep the carton (b) (4) contain important information. ■ store at 20-25°C (68-77°F) <p>Inactive ingredients</p> <p>corn starch, D&C red no. 28, FD&C blue no. 1, FD&C red no. 40, ferric oxide, gelatin, glyceryl monostearate, hydroxypropyl cellulose, hypromellose, magnesium stearate, methacrylic acid copolymer, pharmaceutical ink, polysorbate 80, sucrose, talc, titanium dioxide, triethyl citrate</p> <p>Questions or comments?</p> <p>call toll-free 1-800-XXX-XXXX</p>

- How supplied: Bottle containing 14 capsules. Outer carton will contain 1, 2, or 3 bottles for a total of 14, 28, or 42 capsules (1, 2 or 3 courses of treatment, respectively).
- Container and Closure System: The drug product is packed in 45 mL square shaped bottles made of white high density polyethylene with a (b) (4) screw closure made of (b) (4). Inside the screw closure are a liner and a seal. The liner is made of wax coated (b) (4) and the seal is an aluminum foil lined with (b) (4). The (b) (4) layer is in contact with the product. The seal is induction welded to the bottle for tamper evidence. The (b) (4) screw closure is opened by pressing and turning the cap simultaneously. A desiccant containing (b) (4) is placed inside the bottle.

2 RESULTS

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

2.1 PROMOTIONAL ASSESSMENT

The Division of Nonprescription Clinical Evaluation (DNCE) previously determined the proposed name is acceptable from a promotional perspective under IND 111185. DMEPA concurred with the findings of DNCE's promotional assessment of the proposed name.

2.2 SAFETY ASSESSMENT

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

2.2.1 United States Adopted Names (USAN) SEARCH

The August 15, 2013 search of the United States Adopted Name (USAN) stems identified the USAN stem “-ium” (quaternary ammonium derivatives) in the proposed proprietary name. Although this would normally render the proposed name unacceptable, the root name “Nexium” has been marketed as the proprietary name for this drug product since 2001 and no medication errors related to the “-ium” stem in the Nexium name have been reported. Therefore, we do not find the “-ium” stem to be a cause for rejection in this case.

2.2.2 Components of the Proposed Proprietary Name

Nexium 24HR is comprised of the root name “Nexium” and the modifier “24HR”. The Applicant indicated in their submission that the proposed name, Nexium 24HR, is derived from the currently approved proprietary name “Nexium,” and the intended modifier meaning of “24 hours.” The components of the proposed name (the abbreviation “HR”, the dosing interval “24HR” and the modifier “24HR”) were previously evaluated and found acceptable under IND 111185 in OSE RCM# 2012-2516 dated April 17, 2013.

2.2.3 Medication Error Data Selection of Cases

DMEPA searched FDA Adverse Event Reporting System (FAERS) for medication errors involving Nexium relevant for this review.

The August 15, 2013 search of FAERS used the following search terms in Table 1. The date of the search was limited from the time of last AERS search, December 28, 2012, in OSE Review# 2012-2516.

Table 1: FAERS Search Strategy	
Date	12/28/2012 ~ 8/15/2013
Drug Names	Nexium (Product Name)
MedDRA Search Strategy	Preferred Terms (PT): Wrong drug administered Drug dispensing error Drug label confusion Drug name confusion Drug prescribing error Intercepted drug administration error Intercepted drug dispensing error Intercepted drug prescribing error

Our search retrieved 21 cases. Each case was reviewed for relevancy and duplication. Duplicates were merged into a single case. The NCC MERP Taxonomy of Medication Errors was used to code the case outcome and error root causes when provided by the reporter.

After individual review, 15 cases were excluded from further analysis for the following reasons:

- Adverse event report unrelated to medication error.
- Case related to a patient who ran out of Nexium resulting in dose omission.
- Cases lacking detail narrative for determination if a medication error occurred or not.
- Cases associated with physician off-label prescribing for Nexium at doses higher than 40 mg per day or for twice daily dosing frequency rather than the labeled 10 mg to 40 mg once daily for GERD, risk reduction of NSAID-associated gastric ulcer, and H. pylori eradication.
- Cases reported as intentional drug misuse where patients intentionally took less than prescribed dose of Nexium but the reason for such decision was not provided.
- Wrong dose administration error, where the patient took physician samples of Nexium once daily until she realizes she was prescribed to take the drug twice daily when she filled her prescription and saw the pharmacy dispensed directions. The outcome was reported as unknown. The root cause of this error was likely

the lack of adequate communication between the physician and the patient, thus this case will not be further evaluated.

- Wrong strength dispensing error, in which the pharmacy inadvertently dispensed the 40 mg Nexium oral suspension packets for a prescription of 10 mg Nexium oral suspension packets for a 20 pound child. The outcome was reported as a decrease in urine volume, appeared dehydrated and vomited, but the patient did recover from these symptoms. The proposed OTC Nexium 24HR is a single strength product and will be for sale over the counter instead of stored in the pharmacy next to other strengths of Rx Nexium products. However, we will evaluate the proposed OTC Nexium 24HR container labels and carton labeling to ensure differentiation from the Rx Nexium products in a separate Nexium 24HR labels and labeling review (OSE RCM# 2013-1563).

Following exclusion, six cases of wrong drug medication error remained for further analysis.

Wrong Drug Error (n=6)

- One case reported from a pharmacy after receiving a faxed prescription for “omeprazole” with “Nexium” written right next to it. The reporter concluded that the prescribing physician confused the two drug products to be the same drug. The case narrative did not provide further details on whether the pharmacy contacted the prescriber for a corrected prescription, but it’s likely that the error did not reach the patient since pharmacy already realized the error on the faxed prescription.
- One case described a patient was inadvertently administered intravenous Lasix instead of the ordered intravenous Nexium. A nurse noticed the error after 4 hours of Lasix administration and stopped the infusion. The patient experienced hypokalemia, hypernatremia, and dehydration. The root cause of this wrong drug error was not reported. The proprietary names Nexium and Lasix, as well as the generic names esomeprazole and furosemide, have sufficient orthographic and phonetic differences. Thus, this case will not be further reviewed.
- One case reported a patient who accidentally took Benadryl instead of Nexium because he was too tired. The outcome was unknown. The color of Benadryl tablets (pink or white) differ from the purple Nexium capsules, thus well differentiated. Therefore, this case will not be further reviewed.
- One case described a patient on Nexium at home given Prevacid after being admitted into the hospital. The case narrative did not state whether the hospital physician prescribed Nexium or Prevacid for inpatient use. Furthermore, it’s unclear if Prevacid was given due to hospital formulary reasons or because of an actual inpatient administration error. Thus, this case will not be further reviewed.
- Two cases described a prescription for Nexium dispensed by an outpatient pharmacy as Prilosec/Omeprazole. It’s unclear from the case narrative if such mix up is due to an intended therapeutic substitution because of insurance reasons or due to an actual pharmacy dispensing error. Thus, the cases will not be further reviewed.

Following further analysis, no relevant case was identified for this name review.

2.2.4 FDA Name Simulation Studies

Eighty-one (N=81) practitioners participated in DMEPA’s prescription studies. Sixty-six (n=66) participants from written and voice studies interpreted the name correctly as Nexium 24 HR (“Nexium 24 HR”, “Nexium 24HR”, or “Nexium 24HR UAD”); and an additional three participants (n=3) interpreted the name as “Nexium 24 Hour”. In addition, five (n=5) practitioners from the written studies omitted the modifier “24HR” and interpreted the name as “Nexium”. See Appendix D for the complete listing of interpretations from the verbal and written prescription studies.

2.2.5 Failure Mode and Effects Analysis of Similar Names

Appendix C lists possible orthographic and phonetic misinterpretations of the letters appearing in the proposed proprietary name, Nexium 24HR. Table 2 lists the names with orthographic, phonetic, or spelling similarity to the proposed proprietary name, Nexium 24HR identified by the primary reviewer, the Expert Panel Discussion (EPD), other review disciplines, and from the FDA Prescription Simulation Study. No external name study was submitted.

Table 2. Names with orthographic, phonetic, or spelling similarity to the proposed proprietary name Nexium 24HR

Row	Look Similar					
	Name	Source	Name	Source	Name	Source
1.	(b) (4)	EPD	(b) (4)	EPD	Nexcede	EPD
2.	Nervine	EPD				
	Sound Similar					
	Name	Source	Name	Source	Name	Source
3.	Nebcin	EPD				
	Look and Sound Similar					
	Name	Source	Name	Source	Name	Source
4.	Menrium	EPD	Nexiclon XR	EPD	Nexium IV	EPD
5.	Nexavar	EPD	Nexium	EPD		

Our analysis of the 10 names contained in Table 2 considered the information obtained in the previous sections along with their product characteristics. We determined 10 names will not pose a risk for confusion as described in Appendices E and F.

2.2.6 Communication of DMEPA’s Final Decision to Other Disciplines Following the Promotional and Safety Review

DMEPA communicated our findings to the Division of Nonprescription Clinical Evaluation (DNCE) via e-mail on August 16, 2013. At that time we also requested additional information or concerns that could inform our review. Per e-mail correspondence from DNCE on August 26, 2013, they do not object to the name.

3 FMEA OF RX TO OTC SWITCH

Since the proposed name “Nexium 24HR” utilizes the root name “Nexium”, if the modifier “24HR” is omitted, there is potential for confusion between the Rx Nexium and the proposed OTC Nexium 24HR. However, since Rx Nexium is available in multiple product strengths, the strength would need to be confirmed with the prescriber before dispensing, which should help ensure the consumer receives the intended product.

4 CONCLUSIONS

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

If you have questions or need clarifications, please contact Abiola Olagundoye, OSE project manager, at 301-796-3982.

4.1 COMMENTS TO THE APPLICANT

We have completed our review of the proposed proprietary name, Nexium 24HR, and have concluded that this name is acceptable. However, please note that depending on the review findings of the clinical review division, inclusion of a statement that clarifies the modifier meaning on the container label and carton labeling may be requested. For an example of such a clarifying statement, see the container label and carton labeling for Prevacid 24HR. If the clinical review division determines a similar clarifying statement is required for your product, you will be asked to revise your labels and labeling accordingly. Failure to comply with this request will affect the acceptability of the proposed proprietary name.

The proposed proprietary name must be re-reviewed 90 days prior to approval of the NDA 204655. The results are subject to change. If any of the proposed product characteristics as stated in your July 10, 2013 submission are altered, the name must be resubmitted for review.

5 REFERENCES

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

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

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

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

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

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

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

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

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

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

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

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

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

USPTO provides information regarding patent and trademarks.

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

Clinical Pharmacology contains full monographs for the most common drugs in clinical use, plus mini monographs covering investigational, less common,

combination, nutraceutical and nutritional products. It also provides a keyword search engine.

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

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

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

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

11. Access Medicine (www.accessmedicine.com)

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

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

USAN Stems List contains all the recognized USAN stems.

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

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

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

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

15. Medical Abbreviations (www.medilexicon.com)

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

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

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

17. Walgreens (www.walgreens.com)

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

18. Rx List (www.rxlist.com)

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

19. Dogpile (www.dogpile.com)

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

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

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

APPENDICES

Appendix A

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

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

FDA Adverse Event Reporting System (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FDA implemented FAERS on September 10, 2012, and migrated all the data from the previous reporting system (AERS) to FAERS. Differences may exist when comparing case counts in AERS and FAERS. FDA validated and recoded product information as the AERS reports were migrated to FAERS. In addition, FDA implemented new search functionality based on the date FDA initially received the case to more accurately portray the follow up cases that have multiple receive dates.

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

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

Letters in Name, Nexium 24HR	Scripted May Appear as	Spoken May Be Interpreted as
N	H, M	M
n	h, r, m, u	m
e	a, c, i, o, u, l	a, i, y
x	f, k, v, y	s, z, ks, kz
i	e, j, l	e
u	a, e, n, r, v	oo
m	n, w, z, ar, rn, nn, wi, vi	n
2	Z	--
4	u	--
H	M, N	--
R	B, K, Pr	L

Appendix D: Prescription Simulation Samples and Results

Figure 1. Nexium 24HR Study (Conducted on 7/19/2013)

Handwritten Requisition Medication Order	Verbal Prescription
<p><u>Medication Order:</u></p> <p><i>Nexium 24HR 1 po daily x 14 days</i></p> <p><u>Outpatient Prescription:</u></p> <div style="border: 1px solid black; padding: 5px;"> <p>Patient _____ Date <u>7/18/13</u></p> <p>Address _____</p> <p>R</p> <p><i>Nexium 24HR</i></p> <p><i>UAD</i></p> <p><i>#28</i></p> <p>Refill(s): _____ Dr. <u>OSE</u></p> <p>DEA No. _____ Address _____</p> <p>Telephone _____</p> </div>	<p>Nexium 24 HR</p> <p>The directions for use are Use as directed</p> <p>Dispense number twenty eight</p>

FDA Prescription Simulation Responses (Aggregate 1 Rx Studies Report)

192 People Received Study
81 People Responded

Study Name: Nexium 24HR

Total	33	21	27		
INTERPRETATION	OUTPATIENT	VOICE	INPATIENT	TOTAL	
(b) (4)	0	0	1	1	
NEXIUM	3	0	2	5	
NEXIUM 2.4 HR	0	0	1	1	
NEXIUM 24 HOUR	0	0	1	1	
NEXIUM 24 GIR	0	0	1	1	
NEXIUM 24 HOUR	2	0	1	3	
NEXIUM 24 HOUR DAILY X 14 DAYS	0	0	1	1	
NEXIUM 24 HR	17	14	13	44	
NEXIUM 24HR	9	6	6	21	
NEXIUM 24HR UAD	1	0	0	1	
NEXIUM 34HR	1	0	0	1	
NEXXIUM 24 HR	0	1	0	1	

Appendix E: 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 Nexium 24HR	Failure preventions
1.	Menrium 5-4 Menrium 10-4 Menrium 5-2	Chlordiazepoxide/ Estrogen, esterified	Look	<p>All three products have been withdrawn from the market with no generic equivalents available (NDA 014740 Withdrawn - FR Effective status 4/26/1996). Unable to find the reason for discontinuation, but since no news article can be retrieved from Google search it is unlikely that the product was discontinued due to safety reasons.</p> <p>Additionally, no medication error reports were noted between Nexium and Menrium from post-marketing surveillance and our FAERS search.</p>
2.	(b) (4) ***	(b) (4)	Look	<p>The pair has sufficient orthographic and/or phonetic differences.</p> <p>(b) (4)</p>
3.	Nervine	(b) (4)	Look	<p>The pair has sufficient orthographic and/or phonetic differences.</p> <p>Unable to find product characteristics. Name identified from Clinical Pharmacology (CP), and links to the (b) (4) monograph. However, no actual drug product can be found in CP, Lexi-Comp, or RedBook.</p>
4.	(b) (4)	(b) (4)	Look	(b) (4)

No.	Proprietary Name	Active Ingredient	Similarity to Nexium 24HR	Failure preventions
5.	Nexcede	Ketoprofen	Look	<p>The pair has sufficient orthographic and/or phonetic differences.</p> <p>Additionally, no medication error reports were noted between Nexium and Nexcede from post-marketing surveillance and our FAERS search.</p>
6.	Nexiclon XR	Clonidine	Look	<p>The pair has sufficient orthographic and/or phonetic differences.</p> <p>Additionally, no medication error reports were noted between Nexium and Nexiclon XR from post-marketing surveillance and our FAERS search.</p>
7.	Nexium	Esomeprazole Magnesium	Look & Sound	<p>Name identified from Access Medicine.</p> <p>Nexium and Nexium 24HR could be confused if the modifier “24HR” is omitted from an order. However, since prescription Nexium is available in both 20 mg and 40 mg product strengths, a strength would need to be obtained from the prescriber before dispensing of the product could occur.</p> <p>Nexium is the prescription product where the Clinical Review Division will determine its acceptability for Rx to OTC switch in this review cycle.</p>
8.	Nexium I.V.	Esomeprazole Magnesium	Look & Sound	<p>Name identified from Access Medicine.</p> <p>No medication error reports were noted between Nexium and Nexium IV from post-marketing surveillance and our FAERS search.</p>
9.	Nebcin	Tobramycin	Sound	<p>The pair has sufficient orthographic and/or phonetic differences.</p> <p>Additionally, no medication error reports were noted between Nexium and Nebcin from post-marketing surveillance and our FAERS search.</p>

Appendix F: 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: Nexium 24HR	Dosage Form: Capsules Strength: 20 mg	Usual Dose: 1 capsule by mouth once daily for 14 days
		Failure Mode:	Prevention of Failure Mode:
1.	Nexavar (Sorafenib) Tablets: 200 mg Advanced renal cell carcinoma, hepatocellular cancer: 400 mg by mouth twice daily. Dose adjustment for concomitant CYP3A4 inducers.	Orthographic similarities: The orthographic similarity stems from the root name where both names begin with the same letters (Nex), end in similar letter strings (ar vs. m), share similar number of letters (7 vs. 6) and have similar shapes. Both are single strength and solid oral dosage forms.	Orthographic differences: If included on the order, Nexium 24HR has the additional modifier “24HR” that provides orthographic differentiation from the name Nexavar. Although there appears to be potential for confusion between “Nexavar 200 mg BID” (b) (4) no medication error reports were identified between Nexium and Nexavar from post-marketing surveillance and our 12/28/2012 FAERS search. (Nexavar was approved on 12/20/2005.) Additionally, with the addition of the modifier “24HR” and the OTC switch, we do not expect the introduction of the OTC Nexium 24HR to exacerbate the risk of errors.

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/s/

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