PDUFA PILOT PROJECT

PROPRIETARY NAME REVIEW

CONCEPT PAPER

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I. INTRODUCTION

On September 27, 2007, President Bush signed into law the Food and Drug Administration Amendments Act of 2007 (Pub. L. 110-85, 121 Stat. 823 (FDAAA)), which includes the reauthorization and expansion of the Prescription Drug User Fee Act (PDUFA IV). The reauthorization of PDUFA significantly broadens and strengthens the Food and Drug Administration's (FDA) drug safety program, facilitating more efficient development of safe and effective new medications for the American public. As part of the reauthorization of PDUFA IV, FDA committed to certain performance goals in its goals letter.[1] As one of these goals, FDA stated that it would use user fees to implement various measures to reduce medication errors related to look-alike and sound-alike proprietary names, unclear label abbreviations, acronyms, dose designations, and error-prone label and packaging designs.

In addition, FDA agreed to develop and implement a pilot program to enable pharmaceutical firms participating in the pilot to evaluate proposed proprietary names and to submit the data generated from those evaluations to the FDA for review.[2] In accordance with these goals, FDA has developed and will implement such a pilot program. Using *best practices* when carrying out their own proprietary name reviews and providing FDA with the data that result from those reviews may help pharmaceutical firms choose appropriate proprietary names for their products before application submission. The goals of the program are to minimize the use of names that are misleading or that are likely to lead to medication errors, to make FDA's application review more efficient, and to make regulatory decisions more transparent. At the end of the pilot, FDA will evaluate the results to determine whether the model of industry conducting reviews, submitting the results to FDA, and FDA reviewing the data is feasible and a better model than FDA conducting de novo reviews of proprietary names.

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[1] See goals letter from the Secretary of Health and Human Services to the Chairman of the Committee on Health, Education, Labor, and Pensions of the Senate and the Chairman of the Committee on Energy and Commerce of the House of Representatives, as set forth in the Congressional Record, at http://www.fda.gov/oc/pdufa4/pdufa4goals.html.

[2] For more on FDAAA, PDUFA 4, and the goals letter, *see* http://www.fda.gov/oc/pdufa/default.htm.

FDA has identified the following goals for the pilot program as part of the process of fulfilling the provisions of the goals letter:

1. Hold a public technical meeting (held June 2008) to discuss the planned pilot program and the reviews that will be completed as part of the pilot program
2. Make available by the end of FY 2008 a concept paper describing the pilot and the proprietary submissions that will be made as part of the pilot (this concept paper)
3. Begin enrollment into the pilot program by the end of FY 2009
4. Evaluate the pilot program by the end of FY 2011 (or subsequent to accruing two years of experience with pilot program submissions) to determine whether it is feasible and efficient to have applicants perform their own name analysis and submit resulting data to FDA

II. BACKGROUND

During the past two decades, FDA has considered the role of names and naming processes in medication errors as part of the Agency's focus on the safe use of medical products. FDA has developed internal procedures and processes that are part of its marketing application review process for evaluating the potential for a proposed product name (submitted as part of a new drug application (NDA), biologics license application (BLA), or abbreviated new drug application (ANDA)) to cause or contribute to medication errors. The goal of this pilot program is to test a process that could enable pharmaceutical manufacturers to carry out proprietary name reviews of their products prior to submitting marketing applications to FDA, so that the FDA review of proprietary names would be more efficient.

The following discussion reviews briefly how naming can contribute to medication errors and what recent activities have lead to current efforts to involve product sponsors in the drug name review process.

A. Medication Errors

The FDA uses the definition of a *medication error* as set forth by the National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP). Specifically, a *medication error* is "any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the healthcare professional, patient, or consumer. Such events may be related to professional practice, healthcare products, procedures, and systems, including prescribing; order communication; product labeling, packaging, and nomenclature; compounding; dispensing; distribution; administration; education; monitoring; and use."[3] It is important to note that some medication errors might be preventable

[3] National Coordinating Council for Medication Error Reporting and Prevention (Definition of Medication Error) at http://www.nccmerp.org/aboutMedErrors.html.

events and that the risk of these errors might be detected in the premarket stage of product development using appropriate evaluation methods.

Medication use errors may occur due to sound-alike or look-alike names, unclear labels, or poorly designed packaging.[4] In the U.S. healthcare system, healthcare practitioners rely on a product's name as the critical identifier of the appropriate therapy in a market of thousands of products. Therefore, accurate interpretation of a product's name is essential to ensure that the correct product is procured, prescribed, prepared, dispensed, and administered to the patient. Product names that look or sound alike can lead to medication errors and, potentially, to patient harm by increasing the risk of a healthcare practitioner's misprescribing or misinterpreting the correct product name, dispensing and/or administering the wrong product, or dispensing it incorrectly.

Because product name confusion can occur at any point in the medication use process, FDA considers the potential for confusion throughout the entire U.S. healthcare system, including product procurement, prescribing/ordering, dispensing, administration, and monitoring the effects of a medication.[5]

Medication use within a healthcare organization can be viewed as a system, with several components and processes: inputs (patient and drug therapy information), throughputs (care provided), and outputs (effective, efficient, and safe treatment).[6] Depending on the setting and organization, there are many variables potentially interacting within this system. Such variables may include, but are not limited to:

- Different processes and procedures
- Different types of healthcare practitioners involved
- Different patients
- Different products
- Different storage and dispensing conditions
- Different available technologies
- Different environmental conditions such as lighting, distractions, and workload

Because of the many potential interactions among the system elements, multiple opportunities for medical care-related confusion and medication errors exist.

This concept paper explains how an applicant who chooses to participate in the pilot program could assess a proposed proprietary name for safety (i.e., potential for medication errors), and, at the applicant's option, for promotional implications, before application approval and subsequent

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4 Institute of Medicine, *To Err is Human – Building a Safer Health System (*1999).

5 Institute of Medicine, *Preventing Medication Errors*.

6 Joint Commission on Accreditation of Healthcare Organizations, *Medication Use: A Systems Approach to Reducing Errors*.

marketing of a product in the United States and submit the results of the assessment for review under the planned program, as outlined in the goals letter.

As described more fully in the next section, the evaluation of proprietary names has been discussed numerous times in the past.

B. 2003 FDA Public Meetings on Drug Naming

In June 2003, the FDA, together with the Institute for Safe Medication Practices (ISMP) and the Pharmaceutical Research and Manufacturers of America (PhRMA), held a public meeting to discuss the proper approach to proprietary name evaluation. This meeting was the first public discussion of current methods to screen potential proprietary drug names for similarities to names of currently marketed drugs. Much of the information on the FDA's name evaluation process presented at the meeting is available on the FDA Web site.[7] Specific topics discussed at the June 2003 meeting included:

- The size, qualifications, and best use of internal expert teams to evaluate proprietary names
- Challenges in designing questionnaires for the assessment of proprietary names
- The methodology for conducting a Failure Mode and Effects Analysis (FMEA)
- Handwritten prescription and medication requisition recognition techniques
- Use of computational linguistic methods and string matching to identify sound-alike or look-alike proprietary names
- Sampling frames and methods to identify name evaluation study participants
- Use of computer-assisted decision analysis tools

At the June 2003 public meeting, many meeting participants offered these views:

- Prescription and order simulations should reflect actual situations as much as possible.
- Simulations should replicate medication order situations with known error vulnerabilities.
- The risk of a medication error can be increased or reduced, depending upon how medication orders are communicated (e.g., oral, written, physician order entry, or electronic prescribing).
- Simulations should include not only the product name, but also the strength, route of administration, quantity to dispense, directions for use, and patient age and weight (for pediatric patients).
- Nonprescription (over-the-counter or OTC) drug products should also be subject to the same proprietary name testing standards as prescription drug products.

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[7] *See* http://www.fda.gov/cder/meeting/drugNaming.htm.

More global issues were also discussed at the meeting. Specifically, stakeholders in the drug application process indicated that they consider the current proprietary name testing approach to be only qualitative in nature. The processes and outcomes of the Agency's' proprietary name review were perceived as inconsistent across reviews and FDA approval units, and most of the current approaches to proprietary name reviews could not be validated or reproduced. Because of these issues, the stakeholders and FDA expressed the opinion that there is no *gold standard* for testing proprietary drug product names to assess the risk of error. However, all of the methods discussed were considered to offer value in the name testing process and, in the absence of a *gold standard*, participants stated that multiple tests should be conducted complementarily with a systematic approach, and standardized tools should be applied.

C. December 2003 Meeting

In December 2003, FDA held a meeting of its Drug Safety and Risk Management Advisory Committee (DSARM). At that meeting, the June 2003 public meeting results were reviewed, additional topics in proprietary name evaluation testing were presented, and public comments were elicited. Materials from the December 2003 meeting are available on the FDA Web site.[8]

At the December meeting, the DSARM concluded that, although the current name testing approaches appeared logical and were under refinement, a scientifically valid, outcomes-based, data-driven approach to analyzing proprietary drug product names still did not exist.

D. June 2008 Meeting

A third public meeting was held June 5 and 6, 2008, which focused on subsequent developments in the science and practice of proprietary name analysis since the 2003 meetings, the strength of evidence for the current approaches to name review for both prescription and nonprescription products as discussed in the draft of this concept paper, the elements of *best practice* in testing in the absence of a *gold standard*, and on details of how the planned pilot program should be structured and evaluated. Comments on the proposed pilot were also filed in Docket number FDA-2008-N-0281 after the public meeting.

All of the proposed evaluation methods were judged by individual experts participating in the public meeting to be complementary and considered to offer value in the name testing process. One new method was proposed, Socio-Technical Probabilistic Risk Assessment (STPRA), as an emerging tool for consideration.[9] Many commenters encouraged FDA to incorporate consumers as well as frontline practitioners in every name evaluation. Many commenters also recommended that OTC proprietary names be screened using both consumer and healthcare-based testing because many of these products are recommended by healthcare practitioners and are used in inpatient and long-term care settings.

This concept paper incorporates changes made in response to the comments made at the public meeting or submitted to the related docket. This concept paper contains:

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[8] *See* http://www.fda.gov/ohrms/dockets/ac/03/slides/4007s1.htm.

[9] See http://www.fda.gov/ohrms/dockets/ FDA-2008-N-0281.

(1) A summary of plans and logistics to date on the proposed pilot program

(2) Recommendations, based on FDA's current review processes, on how applicants who choose to participate in the pilot program can assess a proposed proprietary name for safety (i.e., potential for medication errors) and provide that information to FDA.

(3) Recommendations on how pilot participants, may also, at their option, assess and provide information regarding promotional implications of the proposed proprietary name.

(4) A discussion of how the Agency will evaluate the pilot project submissions

Some general information on data sources is provided in the Appendix.

III. PDUFA PILOT PROGRAM—LOGISTICS

As outlined above, one of FDA's performance goals under PDUFA IV is to develop and implement a pilot program that would enable participating pharmaceutical firms to evaluate proposed proprietary names and submit the data generated from those evaluations to the FDA for review. Using *best practices* when carrying out their own proprietary name reviews and providing FDA with the resulting data may help ensure that pharmaceutical firms are able to choose appropriate proprietary names for their products before submitting their applications (e.g., not misleading or likely to lead to medication errors), thus making FDA's application review more efficient and transparent and reducing the likelihood of rejection.

FDA intends the following general plans for the pilot project.

A. What Are the General Logistics of the Pilot Program?

Although procedures for registration for participation in the pilot program are still being developed, FDA expects that enrollment in the pilot program for proprietary name analysis will begin by the end of FY 2009 (September 30, 2009). Participation in the pilot program will be voluntary for applicants, though the FDA expects that many applicants will be interested in participating. To help manage workload, as described below, applicants will be asked contact FDA and register before making their proprietary name submissions. Notice of the procedures will be published and a date for registration to begin will be established.

The FDA hopes that during the two-year enrollment period, 25 to 50 proposed proprietary name submissions will be received and reviewed under the pilot program. To achieve this goal and manage workload within the PDUFA IV timelines, the FDA plans to accept on average one or two submissions per month. The FDA will strive to include a cross-section of applicants that represent large, medium, and small companies. We recognize that some companies may contract this work out to third party vendors. We welcome these submissions. As FDA does not control the selection of these vendors, the pilot program has no mechanism to ensure a wide number of

vendors will be represented in this program. The FDA expects that enrollment will last for two years, after which the FDA will evaluate the pilot program.

For applicants not participating in the pilot program, proposed name submissions will be analyzed and evaluated using FDA's traditional approach to the review of proposed proprietary names.

B. How Will the Pilot Program Function?

Applicants can submit a proprietary name analysis to the FDA (i.e., CDER or CBER) either during the investigational new drug application (IND) process, or as part of the initial submission of the NDA, BLA, or ANDA. Submissions during the IND phase will be accepted ***only*** for products that have completed phase 2 of clinical development.

As soon as an applicant has determined that it would like to participate in the pilot program and has selected a specific proprietary name that it desires to evaluate and submit, the applicant should contact FDA to register and indicate the approximate date of the intended submission. This will enable FDA to manage workflow under the pilot program. . Applicants should then contact the appropriate center 120 days prior to the intended date of the proposed proprietary name submission to discuss specific details of the planned submission.

Applicants can communicate with FDA's project managers regarding questions about their proposed submissions. If necessary, the applicants will be asked to submit their questions in writing; in some cases, a face-to-face meeting to discuss the planned submission may be appropriate.

C. What If I want to Deviate from the Process in the Concept Paper?

Although participation in the pilot program is entirely voluntary, all pilot participants are expected to provide information evaluating the safety (potential for medication error) presented by their proposed proprietary name. Applicants can still participate in the pilot program if they plan to deviate from the proposed proprietary name safety evaluation process outlined in this concept paper and instead use additional or alternative methods. Applicants can also participate in the pilot program without submitting any information to evaluate the promotional implications of their proposed proprietary names (see section IV.B). However, the pilot program will not accept applications that include only an evaluation of the promotional implications of a proposed proprietary name.

For prescription products, applicants should inform the appropriate center at the 120-day pre-submission discussion (recommended above) if they plan to use alternative or additional methods to evaluate the safety of their proposed proprietary name. However, the FDA does not have the resources and, therefore, does not intend to review proposed alternative methodologies with the intent of coming to agreement with an applicant on the appropriateness of these alternative methodologies prior to submission. In such cases, the FDA's review of the alternative methodologies will occur during the review of the actual submission. Consideration will be

given to the strengths and limitations of the alternative method(s) in addition to assessing the adequacy of the data submitted in support of the proposed alternative.

For nonprescription products, FDA encourages sponsors to discuss with the Agency different protocols that could be used for their specific products prior to submission of the proprietary name (see section IV.A.8).

D. Why Do I Have to Make Two Submissions?

For purposes of the pilot program, applicants will be asked to submit two separate sets of drug name-related information to enable the FDA to conduct parallel reviews. The first set should include the applicant's comprehensive evaluation of the proposed proprietary name as described in Section IV of this paper (a recommended template has been provided in Attachment B). The second submission should include the information applicants submit under the Agency's current practice.[10] These two sets of materials will enable FDA to perform two separate, independent reviews in parallel and compare the results as described below.

The first review will evaluate an applicant's proprietary name using the data submitted by the applicant obtained from the test methods outlined in this paper. The second review will independently analyze the proposed proprietary name using the FDA's traditional approach to review of proposed proprietary names. The two reviews will be conducted by two different reviewers, who will not share with each other any details of the data or other findings during the review process. At the end of the review process (i.e., when each reviewer has come to a conclusion regarding the acceptability of the proposed proprietary name), the two reviewers, along with other FDA experts in proprietary name review, will meet to discuss the data and their conclusions. At that time, the two reviewers will note any differences in the data, findings, and conclusions between the two analyses and reviews. Discussion will focus both on the differences in the outcomes of specific analyses, as well as on differences in the overall conclusion regarding the acceptability of the proposed proprietary name. The FDA will exercise its scientific judgment in determining the overall acceptability of the proposed name based on all available data. All noted differences in the specific analyses and conclusions will be shared with the applicant once a final decision has been made.

E. What Happens To My Submission and How Will It Be Reviewed?

Once the FDA receives a proprietary name submission under the pilot program, it will determine if the submission contains the comprehensive information essential for evaluation of the proposed name. A comprehensive submission is one that contains:

- At least one proposed proprietary name
- Identification of the first-choice proprietary name, if more than one name is submitted

[10] FDA is developing guidance on the contents of a complete submission for the evaluation of proprietary names, to address the materials recommended to support review under its current approach.

- Data-driven analyses of the acceptability of the proposed proprietary name, including a clear description of the methods, the data sources, and the raw data
- Information needed to evaluate the proprietary name under the traditional review process (i.e., proposed name, product profile, labels, and labeling)

The FDA will encourage applicants to submit proprietary name evaluations based on the methods set forth in the concept paper. However, an applicant's completion and submission of these evaluations is not necessary for the FDA to consider a submission complete. Applicants can submit alternative evaluations. If, on their face, these evaluations are data-driven, the FDA will accept the submissions. Review of the alternative methodologies will occur during the review of the actual submission.

If the FDA determines that a submission of a proprietary name evaluation is incomplete, it will inform the applicant promptly.

F. Will IND and NDA/BLA Submissions Be Handled Differently?

When the FDA receives a submission of a proposed proprietary name evaluation under the pilot program during the IND phase, it will aim to complete its two independent reviews and arrive at a decision within the review performance goal timelines stipulated under PDUFA IV (180 days from receipt of complete submission, i.e., submission of information needed to evaluate the proprietary name, in 50 percent of cases in FY 2009 and 180 days in 70 percent of cases in FY 2010). When the FDA receives a submission of a proposed proprietary name evaluation under the pilot program at the time an NDA or BLA is submitted, it will aim to complete its two independent reviews and arrive at a regulatory decision within the review performance goal timelines stipulated in PDUFA IV (90 days in 50 percent of cases in FY 2009 and 90 days in 70 percent of cases in FY 2010). Proprietary names submitted as part of an ANDA are not subject to the performance goals stipulated in PDUFA IV, but will be reviewed with a goal of 180 days.

G. What Will the Agency Review in Determining a Proposed Name's Acceptability?

Once the FDA determines that a submission of a proprietary name evaluation contains the comprehensive information essential for substantive review, the parallel reviews will begin. The FDA will assess and review the adequacy of the data from the applicant's analysis and from the FDA's independent analysis. A regulatory decision on the acceptability of a proposed proprietary name will be based on review of all available data (i.e., the applicant's evaluation and FDA's independent analysis). In addition, the FDA will use the data to evaluate the overall pilot program.

H. What If My First Choice Name is Not Acceptable?

Under the pilot program, the FDA will continue its long-standing practice of reviewing the first-choice name. If the FDA determines that the first-choice name is acceptable, the FDA will not review the second-choice name. If the FDA determines that the first-choice name is not

acceptable, the proprietary name review clock established under the goals letter[11] will be stopped. At that time, the FDA will notify the applicant, in writing, of its decision regarding lack of acceptability of the proposed first-choice name. The proprietary name review clock will not re-start until the applicant either has informed the FDA, in writing, that it would like its originally submitted second-choice name reviewed, or until FDA receives an applicant's submission of an alternative second-choice name along with the comprehensive information described below in section III F. At that time, the FDA will begin review of the second-choice name. In the latter scenario, if an applicant has submitted a complete proprietary name analysis for the second-choice name, the responsible center will use discretion to determine whether to review the applicant's analysis in addition to conducting its own analysis using the traditional approach. Although the FDA would ideally review the applicant's completed proprietary name analysis for the second-choice name, factors such as staffing and timelines will be used in making this determination.

I. When and How Will the Pilot Program Be Assessed?

At the end of FY 2011, or subsequent to accruing two years of experience with pilot program submissions, the FDA will evaluate the pilot program to determine whether to have applicants perform their own name analysis and submit resulting data to FDA for review. The FDA anticipates that evaluation of the program will focus primarily on a comparison of the conclusions the FDA has reached after review of applicants' analyses of proposed proprietary names to those the FDA reaches after its own analyses. In addition, the FDA intends to examine patterns, if any, of differences between its analyses and those performed by applicants and between its interpretation of the results of specific applicant analyses, applicants' interpretations of the same results, and the ultimate regulatory decision that was made. The FDA expects that these evaluations will be largely qualitative. Any quantitative evaluations will be descriptive. The results of this pilot program and recommended additions and changes to methods based on the reported results will be discussed in a future public meeting. Following this meeting, draft guidance will be published describing the best test methods for proprietary name evaluation.

IV. ASSESSING PROPOSED PROPRIETARY NAMES IN PILOT PROGRAM

In the following sections, proposals and recommendations about how to assess proprietary names reflect the Agency's thinking and processes as currently practiced. The goals in Section IV are two fold: (1) explain and clarify what the Agency's current assessment involves and (2) recommend approaches pharmaceutical manufacturers should use when performing their assessments under the pilot program.

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[11] See section IX.A. of the goals letter, establishing review performance goals for proprietary names. This proprietary name review clock is distinct from the review performance goal clock for the underlying NDA/BLA submission, addressed in section I.A. of the goals letter.

FDA review of proprietary names includes consideration of both safety and promotional aspects. FDA's primary consideration when evaluating the acceptability of a proposed proprietary name is avoiding the risk of medication errors. This safety review is based on the findings of a Failure Modes and Effects Analysis (FMEA) of the proprietary name. In its safety review, FDA not only considers the potential for a name to be spelled similarly and/or sound similar to the name of a currently marketed product or one that is in the approval pipeline, but also considers the potential for the proposed name to inadvertently function as a source of error for other reasons, such as by suggesting a dosage form or route of administration. Consideration is given to the proposed product's characteristics (including its intended use, dosage form, strength, and route of administration) because the product characteristics provide a context for communication of the product name and ultimately determine the use of the product in the usual clinical practice setting. FDA believes that no single test is sufficient to reach a conclusion that a proprietary name is acceptable. FDA emphasizes that the best approach has proved to be the use of a combination of tests to evaluate name appropriateness.

The promotional review of proposed names considers whether the name functions to overstate the efficacy, minimize the risk, broaden the indication, or make unsubstantiated superiority claims for the product, or is overly "fanciful" by misleadingly implying unique effectiveness or composition . (See 21 U.S.C §§ 321(n), 352(a) & (n); see also 21 CFR §§ 201.10 (c)(3), 202.1(e)(5)(i) &(e)(6)(i).).

The following sections provide a more detailed snapshot of the Agency's proprietary name review. Please note that the promotional assessment of a proposed proprietary name as described in this paper will be optional for applicants participating in the pilot program. If applicants choose not to participate in the promotional review component of the pilot program, the Agency will conduct the promotional review using its traditional approach.

A. Safety Review

FDA's safety review of a proprietary name involves methods that generate a list of names that could be confused with the proposed proprietary name as well as methods to test the likelihood of confusion between these names and the proposed proprietary names.

1. Preliminary Screening

Names often fail FDA's screening process for readily identifiable reasons. Box 1 lists four naming characteristics that when incorporated into a proprietary name, may cause or contribute to medication errors. If a proposed name fails the preliminary screening, it is unlikely to be a viable candidate for a proprietary name. FDA recommends that applicants carefully consider the factors listed in Box 1 in conducting a preliminary screening of their proprietary name for acceptability prior to testing.

Box 1: Naming Characteristics Known to Cause or Contribute to Medication Errors

Dosing Interval
The FDA discourages proprietary names that incorporate or suggest a dosing interval (e.g., NameBID). Drug product characteristics and/or drug release characteristics are subject to change over time with approval of new dosing intervals, thus possibly rendering the original proprietary name misleading.

Dosage Form/Routes of Administration
Generally, the FDA discourages the use of proprietary names that incorporate or suggest a particular dosage form (e.g., Name<u>tabs</u>, Name<u>caps</u>) or route of administration (e.g., Name<u>oral</u>). Avoiding the suggestion of a dosage form or route of administration in the name will enable a company to use the same proprietary name for future dosage forms of the product without making the proprietary name misleading.

Medical And/Or Product Name Abbreviations
The use of common medical abbreviations and coined abbreviations in a proprietary name may be misinterpreted and therefore should generally be avoided. Abbreviations commonly used for prescription communication, especially abbreviations recognized as error-prone and potentially dangerous by the Institute for Safe Medication Practices (www.ISMP.org/tools/errorproneabbreviations.pdf) and the National Coordinating Council on Medication Error Reporting and Prevention (www.nccmerp.org), should be avoided.

Names That Include or Suggest the Composition of the Drug Product
Generally, proprietary names that include or suggest the composition of a drug product may be considered misleading if the proprietary name includes or suggests the name of one or more, but not all, of its ingredients (21 CFR 201.6(b)). In addition, a proprietary name would generally be considered misleading if it includes or suggests the name of an ingredient that is not included in the drug product.

2. USAN Stem Search

In its review of drug names, the FDA screens proposed proprietary names against the stem list created by the United States Adopted Names (USAN) Council. The purpose of the Council is to serve the health professions in the United States by selecting simple, informative, and unique nonproprietary names for drugs products. Selections are made by establishing logical nomenclature classifications based on pharmacological and/or chemical relationships.

The USAN Council (tri-sponsored by the American Medical Association (AMA), the United States Pharmacopeial Convention (USP), and the American Pharmacists Association (APhA)) works closely with the International Nonproprietary Name (INN) Programme of the World Health Organization (WHO) and various national nomenclature groups to achieve global standardization and unification of drug nomenclature and related rules with the goal of ensuring that drug information is communicated accurately and unambiguously.

Because the USAN stems are intended to indicate a pharmacological or chemical trait of a drug, a single stem will be applicable to multiple drug products. Use of these stems in proprietary names, even when used consistently with the USAN meaning, can result in multiple similar proprietary names and proprietary names that are similar to established names, thus increasing the chance of confusion among those drugs. To reduce the potential for confusion, USAN stems should not be incorporated into proprietary names, and FDA recommends that applicants screen potential proprietary names against the USAN stem list, and eliminate those that would incorporate USAN stems.

In evaluating a potential proprietary name against the USAN stem list, the position of the letters that compose the USAN stem is important. For example, the letter sequence "Gli-" only functions as a USAN stem when used as a prefix as defined by the USAN Council. An example of an unacceptable proprietary name including the USAN stem "Gli-" is "**Gli**drug." Conversely, if the same letter sequence that makes up the USAN stem appears in an alternate position in the proposed name, it may be acceptable. An example of a proprietary name including the letter sequence "Gli-" without implicating a confusing use of a USAN stem is "Drug**gli.**" FDA recommends that all proprietary name submissions made under the pilot include a statement indicating that the name does not contain a USAN stem of any size (e.g., does not contain the letter sequence in the position designated as a stem by USAN) and the date on which this information was searched on the USAN list.

3. Orthographic and Phonological Similarities

When reviewing a proposed proprietary name, the centers consider the spelling of the name, pronunciation of the name when spoken, and appearance of the name when scripted throughout the medication use system (e.g., prescribing, dispensing, administering). The staff compare the spelling of the proposed proprietary name with the proprietary and established names of existing and proposed drug products because similarly spelled names may have greater likelihood to sound similar to one another when spoken, or look similar to one another when scripted.

In addition, the centers will examine the orthographic appearance of the proposed name using a number of different legible handwriting samples. Handwritten communication of product names has a long-standing association with product name confusion, often leading to medication errors.

The centers apply expertise gained from root-cause analysis of such medication errors to identify sources of ambiguity within the name that could be introduced when scripting (e.g., "T" may look like "F," lower case "a" looks like a lower case "u," a capital "A" may look like "Ci" or "Cl", a lowercase "en" may look like "ar", "in", or "ea"), along with other orthographic attributes that determine the overall appearance of the product name when scripted (see detail in Table 1 below). Additionally, since spoken communication of medication names is common in clinical settings, the centers compare the pronunciation of the proposed proprietary name with the pronunciation of other product names, accounting for the potential for phonological error due to predictable phonological variance.

The majority of names with similarity to the proposed proprietary name can be identified through database searches. A variety of publicly available databases and resources containing product names can be used to identify similar names. The FDA uses such databases, the Internet, and other printed and electronic drug product resources to search for orthographic and phonological name similarities.

The FDA proposes that applicants also conduct an extensive search to identify any existing names that are similar to the proposed proprietary name or names with orthographic and phonological similarity to the proposed proprietary name. The examples in Table 1 should be useful in this search. It is recommended that applicants search a variety of sources and, at a minimum, search the publicly available databases listed in Appendix A. We recognize that applicants do not have access to proposed proprietary names that are in the FDA review pipeline. Such a limitation will be documented in FDA's final review.

The FDA proposes that applicants submit the following information with their applications:

- All search queries
- The system parameters used for each search (e.g., letter substitution)
- The precise databases searched
- Any thresholds imposed on the output (e.g., top 100, top 200, etc.)
- The date the search was conducted or the last update of the database that was searched
- Pooled results with source citation and full product characteristics of each name identified as a possible source of confusion with the proposed name.

Note: Although such searches generate many names that may be ruled out under further analysis, we request that applicants submit all names originally identified as potentially similar to the proposed name.

Table 1: Criteria Used to Identify Product Names that Look or Sound Similar to a Proposed Proprietary Name			
Type of similarity	**Considerations when searching the databases**		
	Potential causes of product name similarity	**Attributes examined to identify similar product names**	**Potential Effects**
Look-alike	Similar spelling	Identical prefix Identical infix Identical suffix Length of the name Overlapping product characteristics	Names may appear similar in print or electronic media and lead to product name confusion in printed or electronic communication Names may look similar when scripted and lead to product name confusion in written communication
	Orthographic similarity	Similar spelling Length of the name Upstrokes Downstrokes Cross-stokes Dotted letters Ambiguity introduced by scripting letters Overlapping product characteristics	Names may look similar when scripted, and lead to product name confusion in written communication
Sound-alike	Phonological similarity	Identical prefix Identical infix Identical suffix Number of syllables Stresses Placement of vowel sounds Placement of consonant sounds Overlapping product characteristics	Names may sound similar when pronounced and lead to product name confusion in spoken communication

4. Computational Methods

To complement the above-delineated process, FDA may use a computerized method to identify any phonological and orthographic similarities between product names. FDA recommends that applicants use such a program. Although these computerized methods are useful in hypothesis generation (i.e., developing the list of possible names that could be confused with the name under review), they should not be used for the more complex task of hypothesis testing (i.e., evaluating which names have potential for error and harm). No single method can evaluate all dimensions of similarity, nor will any single measure perform as well an intelligently assembled combination of measures (e.g., one that integrates measures of orthographic, phonological, and semantic similarities).

There are reasons why computerized methods and algorithms are not useful for hypothesis testing. First, programs that use String-edit distance and Bigram pairs do not fully evaluate the similarity of names, particularly with respect to orthographic appearance. Predictions based on computerized measures of similarity will occasionally yield both false positive predictions (i.e., saying a pair is confusing when it is not) and false negative predictions (i.e., saying a pair is not confusing when it really is).

Although the computerized methods and algorithms provide reproducible measures of similarity or dissimilarity, these measures are difficult to interpret when the scores reveal moderate similarities or dissimilarities between the names.

The FDA proposes that applicants use computerized methods and algorithms that can detect the similarity of product names from a phonological perspective, orthographic perspective, or both. In submitting computational data, the FDA recommends that applicants provide the following information:

- The measure of similarity/distance used
- The values assigned to any adjustable parameters
- The manner in which non-name attributes (e.g., strength, dosage form, route of administration) were handled
- If a weighting scheme was used, describe how the different elements were weighted
- The precise database searched (e.g., Orange Book, including or excluding discontinued products, USPTO (what class), Multum Lexicon).
- If a cutoff or threshold was used to narrow or widen the search results, the cutoff or threshold, and how and why it was chosen
- Testing output

5. Medication Error Data

FDA believes that data obtained from case reports of medication errors help to inform the analysis of a proposed proprietary name and overall product design (e.g., packaging, labels, and labeling). The FDA searches databases containing medication error reports with the goal of identifying relevant information about potential errors before approval.

FDA recommends that when a proposed product contains an active ingredient that is marketed domestically or abroad, all available information relevant to medication error cases associated with that active ingredient be identified and submitted to the FDA. Applicants can obtain medication error report information from their own safety databases. Medication error report data also can be obtained from published literature, and any other relevant databases (e.g., data collected by other regulatory authorities as set forth in Appendix A).

Relevant information would include any error reports related to the product nomenclature (established and proposed proprietary name), product design, label, and labeling. This information should be identified and reported to the FDA in line listings with a narrative as described in Box 2.

Box 2: Format for Submitting Relevant Information

- The FDA recommends that applicants submit a line listing and narratives of the medication error case reports identified in the postmarket period for marketed products with the same active ingredient as the product under review.
- The applicant should cite the source of the report along with any analysis conducted by the applicant.
- Applicants should submit the full text of any article published on medication errors associated with the product.
- Applicants should also categorize these errors by type (e.g., incorrect product, incorrect route of administration) using the NCC MERP taxonomy.
- Applicants should review these cases to identify factors that contributed to the medication errors and to ascertain whether these risks apply to the proposed proprietary product name. All medication error data should be integrated into the FMEA.

6. Name Simulation Studies

FDA performs limited internal simulation studies to test the response of healthcare practitioners to proposed names. FDA believes that applicants should consider the following elements when planning the use of simulation studies.

a. General description

Generally, name simulation studies test the response of practitioners to a proposed name by asking them to use the name in simulated real-world conditions. The more closely the simulation approximates real use conditions, the more valuable the simulation. At a minimum, certain characteristics of real use conditions are easily simulated and should be present (e.g. in the use of lined paper, prescription pads, and telephone orders to approximate inpatient written, outpatient written and outpatient verbal prescribing, respectively, and the use of background noise, different handwriting samples, different color inks, directions for use, and different voices/accents to mimic the diverse prescribing conditions). Additionally, the simulation study should present the name with the corresponding product characteristics (e.g., strength, route, dosing, and frequency) that are likely to be used to communicate prescriptions and orders for the proposed product.

b. Study design

A simulation study designed to detect close to a zero percentage error rate with statistical significance would require an extremely large sample size (e.g., a sample of ~26,000 would be

required to detect an error rate of 0.001 at the 0.05 significance level[12]). We recognize that a study of this magnitude is not realistic. However, we may be able to understand how a proposed name might perform in real world conditions through a well-designed parallel group observational study. In such a study, each group represents different prescribing scenarios based on all of the potential prescribing conditions for the proposed product (e.g., for an inpatient written order, an order written by a physician using lined paper, transcribed and entered into a computer by a unit clerk, read and dispensed by a pharmacist, read and administered by a nurse). When performing simulation testing, both quantitative and qualitative data should be collected. Both types of data can be collected anywhere in the medication use system. For example, quantitative data might document how many times a participant interpreted a prescription correctly and how many times it was misinterpreted. The qualitative data would include any concerns or problems the participants thought of or encountered while going through the process (e.g., no error occurred but a participant felt that there could have been an error in a different situation).

c. Participants

All participants in name simulation studies should be active practitioners, such as prescribers, transcribers, dispensers, or administrators of drugs in the proposed prescribing condition for the product, and should be representative of the full range of persons involved, including physicians, physician assistants, nurse practitioners, nurses, pharmacists, pharmacy technicians, ward clerks, and other relevant individuals.. All settings (e.g., community pharmacy, ambulatory care, hospital, long-term care) where the product could be used should be considered. For example, if a product will be prescribed by private practice oncologists, the participants should include, but not be limited to, private practice oncologists, nurses working in this private practice setting, and other individuals who might call in a prescription from this setting. If the product will be dispensed in an inpatient setting, the participants should include, but not be limited to, inpatient pharmacists, pharmacy technicians, ward clerks and nurses. Consideration should be given to including primary care practitioners, pharmacists, and nurses even when evaluating names of specialty drugs to probe what medication names outside the specialty might cause error. These stakeholders will bring experience from different workflow and practice environments.

Patients should be included in Failure Mode and Effects Analysis for all products (see section 7). However, the FDA does not generally consider it necessary to include patients in a name simulation study for a prescription product that is simulating use in an inpatient setting because patients are not involved in the prescribing, dispensing, and administration of medications in this setting of care.

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12 This calculation was made to determine whether the error rate differs from 0.001 at a 0.05 significance level and 80% power, assuming the medication error rate of the sample is 0.0005.

d. Number of scenarios

The FDA recommends that a minimum of 20 scenarios representing each possible prescribing condition for the proposed drug be performed to provide an adequate descriptive assessment (e.g., communication from physician to ward clerk to pharmacist to nurse). Participants involved in a name simulation study can participate in the testing of an unlimited number of proposed proprietary names. However, to minimize bias, a name should not be tested by the same participant more than once. The number of participants in each simulation scenario should reflect the actual number of participants in an actual clinical scenario. Generally, these scenarios will involve 2 to 5 participants (e.g., physician—ward clerk—pharmacist—nurse). Table 2 provides 20 scenarios that could be used for an inpatient setting. We estimate that approximately 70 participants will be needed because not all scenarios will involve the same number of participants (e.g., physician—pharmacist).

Each possible prescribing condition for the proposed drug should be tested several times giving consideration to all modes of communication (e.g., spoken, written, computer order entry, computer selection and selection of drug from drop down menu) (see examples Table 2 below). For example, for a drug that is administered only intravenously in an inpatient setting, an outpatient simulation using a handwritten prescription may not be helpful because this product would not be typically used in this setting of care. A simulation for an orally administered drug that could be dispensed in both in- and outpatient settings should contain all possible inpatient and outpatient scenarios. Table 2 shows example scenarios for an orally administered drug. These example scenarios should be revised to reflect the likely setting(s) of care for the product and be specific to how the applicant's product will be prescribed, transcribed, dispensed, and administered in the real-world condition.

Applicants should consider embedding the test name in a list of two or three other test names of marketed drugs in the simulated prescriptions, or consider other simulated prescription formats that are designed to mimic the results of real-world settings. Spoken orders should include several scenarios with an unaided pronunciation and several scenarios with a pronunciation based on how the applicant proposes to pronounce the name when marketed (e.g., "Kaletra" is pronounced by some as Kuh-let-ra and the applicant's pronunciation is Kuh-lee-tra).

Table 2:
Example Scenarios for Name Simulation Study for an Orally Administered Drug

Scenario Number	Prescribing Condition	Participant Group
1	Inpatient: Written order on lined paper	physician A - ward clerk A – nurse A - pharmacist A - nurse B
2	Inpatient: Written order on lined paper	physician assistant A - ward clerk B – nurse C - pharmacist B – nurse D
3	Inpatient: Written order on lined paper	physician B – nurse E – pharmacist C – nurse F
4	Inpatient: Written order on lined paper	physician C - ward clerk C – nurse G - pharmacist D – nurse H
5	Inpatient: Spoken order transcribed to a written order unaided pronunciation	physician D – nurse I - ward clerk D – pharmacist E – nurse J

Table 2: **Example Scenarios for Name Simulation Study for an Orally Administered Drug**		
Scenario Number	**Prescribing Condition**	**Participant Group**
6	Inpatient: Spoken order transcribed to a written order unaided pronunciation	physician assistant B – nurse K - ward clerk E – pharmacist F – nurse L
7	Inpatient: Spoken order transcribed to a written order pronunciation as intended by applicant	physician E – nurse M – pharmacist G – nurse N
8	Inpatient: Spoken order transcribed to a written order pronunciation as intended by applicant	physician F – nurse O - ward clerk F – pharmacist H – nurse P
9	Inpatient: Direct computer entry	physician G - pharmacist I - nurse Q
10	Inpatient: Direct computer entry	physician assistant C - pharmacist J - nurse R
11	Inpatient: Direct computer entry	physician H - pharmacist K - nurse S
12	Inpatient: Direct computer entry	nurse practitioner A - pharmacist L - nurse P
13	Outpatient: Written prescription	nurse practitioner B - pharmacist M
14	Outpatient: Written prescription	physician I - pharmacist N
15	Outpatient: Written prescription	physician J - pharmacist O
16	Outpatient: Written prescription	physician assistant D - pharmacist P
17	Outpatient: Spoken prescription left on voice mail unaided pronunciation	nurse practitioner C - pharmacist Q
18	Outpatient: Spoken prescription left on voice mail unaided pronunciation	physician K - pharmacist R
19	Outpatient: Spoken prescription left on voice mail pronunciation as intended by applicant	nurse practitioner D - pharmacist S
20	Outpatient: Spoken prescription left on voice mail pronunciation as intended by applicant	nurse practitioner E – pharmacist T
21	Outpatient: Electronic generated prescription	physician L – pharmacist U
22	Outpatient: Electronic generated prescription	physician M – pharmacy technician A – pharmacist V
23	Outpatient: Electronic generated prescription	physician assistant E – pharmacist W
	Total Participants	70

Each participant should be interviewed at the end of the simulation using nonleading scripted follow-up questions. Responses should be recorded verbatim. All qualitative data derived from follow-up questioning should be coded and analyzed based on verbatim responses from the participants (Table 3). When the results are submitted to FDA for review, the raw data should include the coded responses as well as all the verbatim data.

Table 3: Examples of Coded Responses to Follow-up Questions		
Follow-up Questions	**Coded responses**	**Participants with coded response**
Do you think this name looks like any other drug name? If yes which drug?	Yes No Brand X Brand Y	8 52 3 5
Do you think this name sounds like any other drug name? If yes, which drug?	Yes No Brand X	8 52 8
Do you think this name looks like any medical terms or laboratory tests? If yes, what terms or tests?	Yes No	0 60
Do you think this name sounds like any medical terms or laboratory tests? If yes, what terms or tests?	Yes No	0 60
Describe your overall impression of the name. These comments do not necessarily have to be related to safety.	There are many drug names on the market that seem to start with ___. Good name does not appear to be a problem The name seems to conflict with what the drug is suppose to treat	12 35 13

Transparency of the study process is essential. Applicants should submit, and the FDA will review, all methodology associated with the simulation study—including but not limited to how participants were chosen and the composition and qualifications (e.g., current roles in clinical practice) of participants.

7. Failure Mode and Effects Analysis

Failure Mode and Effects Analysis (FMEA) is a systematic prospective method the FDA uses to examine the nomenclature, labeling, and packaging for possible ways in which a failure (i.e., an

error) can occur.[13] Postmarket experience has shown that the nomenclature and design of the label/labeling and packaging of a product directly contributes to the occurrence and the likelihood of medication errors.

FMEA capitalizes on the predictable and preventable nature of medication errors and enables the identification of failure modes prior to approval, when actions to overcome these issues are easier to implement than remedies available in the postapproval phase. When performing a FMEA of a proposed product, the FDA considers the use of the product at all points in the medication system. Applicants should do the same. Because the proposed product is not yet marketed, the applicant should anticipate the use of the product under the proposed prescribing conditions by considering the intended indication and product characteristics. The applicant should then consider the proposed product in the context of the usual practice setting and work to identify potential failure modes and the effects associated with the failure modes.

a. Identifying failure modes

To identify potential failure modes, the applicant should compare the proposed proprietary name to all of the names gathered during the safety review. The applicant should consider the vulnerability of the proposed name to misinterpretation and confusion and ask the following questions:

- Could the similarity of this proposed proprietary name to other proprietary names cause the names to be confused with one another at any point under the proposed prescribing conditions? As a guide to answering this question, one should consider the similarity or dissimilarity of the names in question in their entireties as to spelling, appearance, sound, connotation, and commercial impression.

  Are there other aspects of the proposed proprietary name, unrelated to the orthographic and phonological similarity that could be potentially misleading and cause confusion at any point under the proposed prescribing conditions? Such errors may not necessarily involve confusion between the proposed drug and another drug product. For example, the FDA has learned that a proposed name for a multi-ingredient product that represents only one of the active ingredients contained in the product[14]; names that may encode a frequency or route of administration inconsistent with the actual product characteristics; or names that look or sound like other medical terms, diagnostic tests, and abbreviations are name characteristics that could cause confusion and lead to medication errors.

An applicant should support a "no" answer to either or both of these questions by providing FDA with its raw data and a summary of the basis for its conclusion that the name is not confusingly similar to any other names or will not otherwise cause medication error; however, for a "no" answer, the applicant need not go on to conduct the analysis described in next section of this

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[13] Joint Commission Resources, Root Cause Analysis in Healthcare 201 (3d ed, 2005).

[14] See 21 CFR 201.6(b), establishing that labeling may be misleading if the name of the drug includes or suggests the name of one or more but not all of its ingredients.

paper. A response of "yes" to either of the above questions indicates a failure mode and represents the potential for a proposed proprietary name to lead to confusion and misinterpretation. In the case of a "yes" answer, the applicant should proceed to conduct the evaluation described in the following section.

b. Identifying failure effects

If the answers to the either of the aforementioned questions is "yes," the next step in the FMEA is to evaluate all potential failure modes. The potential failure modes are evaluated to determine the likely *effect* of the confusion, by asking the following question:

- Could this confusion result in medication errors in the usual practice setting?

The answer to this question is a central component of the FDA's overall risk assessment of the proposed proprietary name. If the FMEA determines that the source of confusion is unlikely to ultimately cause medication errors under the proposed prescribing conditions, the proposed name and findings should be submitted to the FDA for further review.

If the FMEA determines that the proposed proprietary name could be a source of confusion that could cause medication errors under the proposed prescribing conditions, an alternate proprietary name should be evaluated.

In certain instances, the FMEA findings may suggest other risk-reduction strategies, such as product reformulation to avoid an overlap in strength or an alternate modifier designation that may reduce the risk of medication errors resulting from product name confusion. Alternatively, the applicant may try to justify why the finding might not lead to a medication error or why the risk of medication error with the proposed name is less than risks associated with other alternative nomenclature options.

c. FMEA team

Selection of the FMEA team is a critical step in the FMEA process. The team should be multidisciplinary to ensure that different perspectives and viewpoints are brought to the process. The team should include a representative sample of practicing health professionals of varying clinical backgrounds, disciplines, and experience who would be procuring, prescribing, dispensing, and administering the product under evaluation as described in Section IV.A.6.c. above. If a product will be dispensed in an outpatient setting, the team should also include a patient. The FMEA team should include health professionals with experience in actual-use settings and members with expertise in the field of medication error prevention. FMEA teams typically consist of 8 to 12 members.[15]

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[15] Joint Commission on Accreditation of Healthcare Organizations, Failure Mode and Effects Analysis in Health Care: Proactive Risk Reduction 27 (2005).

The FDA will review the methodology associated with the FMEA including how the team was chosen, the composition of the team and qualifications (e.g., current roles in clinical practice) of its members, the failure modes identified, and any proposed risk mitigation strategies.

The step-by-step FMEA analysis, conclusions, and rationale should be submitted to the FDA as part of any proposed proprietary name submission under the pilot program.

8. Nonprescription Drug Products Analysis

The proposed proprietary names of nonprescription drug products (also known as over-the-counter (OTC) drugs) submitted for approval under an NDA or ANDA are assessed prior to approval of the drug, as part of the review of the complete product labeling (see 21 CFR 314.125(b)). Consumer safety issues are given particular consideration in the labeling evaluation of these products. Under the pilot program, OTC product names should be assessed using the methods described in Sections 1-7 above, taking into account the following considerations.

- OTC drugs are routinely selected and purchased by consumers and often recommended by name to consumers by a healthcare practitioner. For these reasons, names for OTC drugs should be evaluated using simulation studies designed to test both consumer and healthcare professional understanding of proposed proprietary names. It may be important to evaluate whether participants can interpret written and oral communication of the name to safely select the proposed product.

- FDA regulations (21 CFR 201.60, 201.61 and 201.62) outline the type of information that is required on the principal display panel of an OTC drug product. This information is important so the consumer can accurately self select and use the product, and as such, should not be misleading.

- Although some packages may adhere to these regulations regarding the content of the principal display panel, in addition to the proprietary name, the presentation of information on the package may be inadequate and lead to consumer confusion, resulting in medication errors.

- Concerns include, but are not limited to: information may be presented in a confusing manner; the package may lack necessary information for proper use; or there may be a failure to present the information so a consumer can differentiate the product from other similar products and use it correctly.

- When a proprietary name is the name of a family of products, with multiple product names differing only by the suffix, it is even more important that the information on the principal display panel enable the consumer to differentiate products at the point of purchase. Even distinguishing information elsewhere on the outer carton labeling may be overlooked.

- There are a number of examples to illustrate potential problems. Companies have used the same proprietary name for single ingredient and combination products containing different active ingredients, or the same name for different combinations, causing consumers to purchase the wrong product.

- FDA is also aware of consumer confusion resulting from the use of proprietary names that differ only by the suffix attached to them to designate a variety of combination drug products, containing up to four ingredients (e.g., OURDRUG PM, OURDRUG. Cough and Cold formula.) When the same proprietary name is used for products containing different active ingredients, studies should be conducted to determine whether consumers are able to differentiate these products with the same proprietary name, with or without a suffix, based on the other information on the principal display panel.

It is difficult to design a single study that could address all possible scenarios. Thus, FDA encourages sponsors to meet with the Agency to discuss different protocols that could be used for their specific products prior to submission of the proposed proprietary name. We recognize that the design of the studies may need to differ depending on the issues affecting a proposed product.

The following general principles should be applied when testing a proprietary name of an OTC drug product in consumer and healthcare professional populations:

- The evaluation should assess whether or not a proprietary name exaggerates the safety or effectiveness of the product or is otherwise confusing or misleading. Aspects to consider include whether or not a proprietary name implies an indication or use, active ingredient, dosing frequency, population, route of administration, and duration of effect that is inconsistent with the proposed dosing frequency, population, route of administration, and duration of effect of the product.

- Evaluation questions should be nonleading and filter questions should be incorporated into the questionnaire (e.g. “Does the name tell you what the product is used for?”, yes or no. If yes, “what does it tell you it is used for?”)

B. Promotional Review (Optional)

The FDA 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. See 21 U.S.C §§ 321(n), 352(a) & (n); see also 21 CFR §§ 201.10 (c)(3), 202.1(e)(5)(i) &(e)(6)(i).

1. Participation in the Promotional Review Element of the Pilot Program

As previously noted, an applicant who chooses to participate in the pilot program may do so without submitting information regarding the promotional implications of its proposed proprietary name; pilot participation requires only the submission of safety review information. FDA will conduct its customary promotional review whether or not an applicant submits its own promotional review. Sponsors who choose to participate in the promotional review aspect of the proprietary name pilot program may do so either (1) as part of an initial proposed proprietary name submission made under the pilot, or (2) as part of a response to FDA's rejection of a proposed proprietary name submitted under the pilot (where the initial submission addressed only safety review).

2. Evaluation

If an applicant chooses to conduct a promotional review, the promotional and safety reviews should be performed independently from one another so as to minimize bias in either review. The promotional review should focus on avoiding names that overstate product efficacy or safety, expand product indications, suggest superiority without substantiation, or that are of a fanciful nature that misleadingly implies unique effectiveness or composition . It would be desirable for the promotional evaluation to involve personnel from marketing, regulatory affairs, social scientists with expertise in consumer psychology, and legal staff to determine whether a proposed proprietary name contains misleading implications. The company's evaluation team should include persons versed in the regulations that govern prescription product advertising and promotion, with experience in the process of reviewing proposed promotional materials and proposed proprietary names.[16] The analysis of sound empirical data, if available, should be given prominence in the evaluation of proposed proprietary names.

To increase transparency and predictability in the review of proposed proprietary names from a promotional perspective, the FDA has proposed a quantitative evaluation method. The design and methodology of studies used for this evaluation should be valid and reliable. To facilitate collective evaluation at the end of the pilot program, it would be helpful for these studies also to use the same measures. Although development of standardized, validated questionnaire measures (i.e., standard questions to be used across all studies) is thus desirable, it is beyond the scope of this concept paper.[17] One possible study methodology and some sample questions are included below. These question samples are designed to guide sponsors in the development of outcome measures in their studies but are not intended to be an exhaustive list. Sponsors are encouraged, but not required, to seek advisory comments from the Agency on their proposed study methodology, questionnaire, and analysis plan prior to data collection.

3. Research Methodology

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16 A company's internal process for selecting among potential names is not intended to be part of the submission. The company's submission should address only section B.3. Methodology.

17 Frameworks for designing a study to examine the potential promotional implications of proposed proprietary names are available. See, for example, Whitley, Jr., B.E. (1996). *Principles of research in behavioral science.* Mountain View, CA: Mayfield Publishing Company.

The FDA recommends an experimental approach to evaluate promotional implications of proposed names because this method enables interpretation of causal relationships between variables. That is, by controlling all other experimental factors besides the drug name, researchers can be confident that the name itself caused particular responses. Box 3 provides one possible approach for such an evaluation. Other approaches may be appropriate.

The approach described in Box 3 should be especially helpful in gathering information about how a name influences attitudes and behaviors of practicing healthcare practitioners. If participants are only asked what they think about the proposed name, it will be difficult to determine how accurately their responses reflect their actual thoughts or likely behaviors because participants may state what they think they should state or what they think the investigators want to hear. By comparing the responses to the proposed name with responses to the neutral control name, however, it could be determined whether the proposed name actually does influence these thoughts and intended behaviors.

a. Design of Questions

A combination of open-ended and closed-ended questions, arranged from more general to more specific, should be used. Questions should be designed so as to avoid leading questions, yea-saying and other forms of bias.[18] Initial questions in the study should be asked before participants have any information about the product so that the answers will not be influenced by knowledge of product characteristics. Subsequent questions would be asked after receiving indication information for the product but no other identifying information. Because IND studies themselves form the basis of ultimate determinations about the efficacy and risk of a drug product seeking approval, the specifics may not be known at the time the proprietary name is proposed and undergoing testing. Thus, there should be a measure of participant response when they have only minimal information.

[18] For a brief discussion of questionnaire bias in label comprehension studies, see Morris, L.A., Lechter, K., Weintraub, M., and Bowen, D. (1998). Comprehension testing for OTC drug labels: Goals, methods, target population, and testing environment. *Journal of Public Policy and Marketing*, *17*(1), 86-96.

Box 3: Possible Evaluation Design

The FDA proposes a crossover design in which the proposed proprietary name is evaluated in the context of both a neutral control name and an extreme control name. This involves splitting the sample into two groups, both of whom will evaluate the proposed proprietary name but in a different order from each other.

Before testing the proposed proprietary name, two control names should be established through pretesting:

A ***neutral control name*** that is pretested to ensure that it makes no representations at all (i.e., it is neutral from a promotional standpoint) should be established.

An ***extreme control name*** that is pretested to ensure it makes clear misrepresentations should be established

The entire sample will respond first to questions about the neutral control name, described above. Next, half of the sample responds to the proposed name and then to the ***extreme control name*** described above. The other half of the sample responds to this ***extreme control name*** first and then to the proposed name.

The study questions used as outcome measures should cover perceptions elicited by the proposed name that are of a promotional nature (e.g., product safety, efficacy, indication, superiority), as well as questions designed to elicit aspects of behavioral intent (e.g., likelihood to prescribe). The comparison of interest is participant responses to the proposed name compared with responses to the neutral control name. The extreme name serves as a positive control to ensure that individuals can identify names that make representations about efficacy, safety or other promotional aspects.

The FDA suggests that the neutral and extreme names be fictitious in nature to control for participants' prior experience and attitudes. Existing names could be acceptable as neutral or extreme controls if they are pretested and shown to possess the desired experimental qualities outlined above.

Sponsors may choose to select different neutral and extreme control names for each study or they may choose to use the same neutral and extreme control names for multiple studies. Respondents should be exposed to the neutral control name only once across studies: that is, sponsors that choose to use the same neutral name in more than one study should choose a new test sample for that study to ensure that participants have not previously responded to the neutral name.

Examples of questions include:

- You have just learned of a new product named *DRUG X*. What, if anything, does the name *DRUG X* say or suggest to you about the product? (*open-ended question*)

- Based on this name, which of these conditions do you think DRUG X treats? (please choose the best answer) (*closed-ended question)*
  - Condition 1
  - Condition 2
  - Condition 3
  - Condition 4

- Based on this name, how effective or ineffective would you say DRUG X is?

- Very effective
- Somewhat effective
- Somewhat ineffective
- Very ineffective

- Based on this name, how safe or unsafe would you say DRUG X is?
  - Very safe
  - Somewhat safe
  - Somewhat unsafe
  - Very unsafe

- Now you learn that the product *DRUG X* is used to treat CONDITION Y. What does this name mean to you in this context?

- Based on this name, how safe or unsafe would you say it is to use DRUG X to treat CONDITION Y?
  - Very safe
  - Somewhat safe
  - Somewhat unsafe
  - Very unsafe

- Based on this name, how effective or ineffective would you say DRUG X is to treat CONDITION Y?
  - Very effective
  - Somewhat effective
  - Somewhat ineffective
  - Very ineffective

- If DRUG X were available, how likely would you be to prescribe DRUG X for CONDITION Y?
  - Not at all likely
  - Somewhat likely
  - Moderately likely
  - Very likely

- On a scale from 1 to 5 where 1 equals *Strongly Disagree* and 5 equals *Strongly Agree*, please indicate your agreement or disagreement with the following statement:

  This name makes superiority claims over other products with the same indication.

b. Sampling

Note: these are general comments. A statistician should be consulted before making definitive determinations about sample size and sampling design. The size of the sample should be adequate to detect differences. The sample should represent the relevant prescribing population

and be generalizable to this population. In addition, applicants should also consider testing a sample of consumers. Although this group does not have prescribing authority, consumers should and do participate actively in treatment decisions. The product name may play a role here through direct-to-consumer (DTC) advertising.

c. Submission to FDA

Sponsors choosing to participate in the promotional review component of the pilot program should submit to the appropriate center for evaluation all research methodology used to support a proposed proprietary name. This includes a description of participant demographics; the product profile provided to study participants; the complete study questionnaire; the coding scheme used to analyze open-ended questions; complete study results (both positive and negative), including results of pretests; and any other information given to the study participants regarding the drug approval process (e.g., copies of FDA regulations given to study participants).

V. WHAT WILL FDA CONSIDER WHEN EVALUATING PILOT SUBMISSIONS?

This section describes the kinds of things the FDA will consider as it reviews manufacturers' submissions as part of the pilot program.

A. Standards

The ultimate goal of FDA's safety review of a proposed proprietary name is avoiding medication errors. The FDA will evaluate the safety and promotional implications of a name under the pilot program using the same methods the Agency currently uses to evaluate proposed proprietary names. If a proprietary name demonstrates vulnerability to confusion in the testing stage, the FDA will not recommend its approval for use in the market and will request the applicant propose an alternate name for evaluation. There is no apparent health benefit from using one name rather than another. From a public health perspective, then, any preventable risk of medication error that can be identified prior to drug approval should be addressed by selection of an alternative name if necessary and sufficient to avoid similar risk.. The FDA will examine both the process used and the reasoning and conclusions reached in an applicant’s determination that the name it puts forth is safe, and, if addressed by the applicant, that the name does not have impermissible promotional implications.

B. Assessing the Data, Methods, and Evaluation

Under the pilot program, the FDA will assess the adequacy of the data collected and submitted to support the safety and promotional analysis, including any data derived from alternative methods. We will also identify medication error safety concerns that will need attention prior to approval. Because the FDA will also evaluate the safety and promotional aspects of the proposed name using our traditional proposed drug name review, we intend to evaluate and document the differences in the data, findings, and conclusions between the center’s and applicant’s analyses and reviews.

At the end of the pilot, FDA will evaluate the results to determine if the methods described in this paper are reliable, if methods should be changed or added, and if the model of industry conducting reviews, submitting the results to FDA, and FDA reviewing the data would be a better model than the current model. FDA will present these findings in a public meeting in FY 2013 or before.

As a general guide, we plan to consider the following:

1. Did the applicant screen the proposed name with regard to the common errors listed previously (Box 1) to ensure acceptability for testing?
2. Did the applicant confirm that the proposed name does not contain a USAN stem; was the date of the search included?
3. Did the applicant conduct a thorough database search to identify existing similar names, using, at a minimum, those publicly available databases described in Appendix A? Was the search methodology adequately described, and were all resulting similar names documented?
4. Did the applicant use appropriate computational methods to identify additional look-alike and sound-alike names? Were the parameters adequately described?
5. Did the applicant consider all available medication error data related to the proposed proprietary name (e.g. for products with the same active ingredient marketed domestically or internationally)?
6. Did the applicant conduct a name simulation study that reflected all relevant real-use conditions (e.g., inpatient/outpatient, written/spoken)? Were all resulting qualitative and quantitative data from the simulation provided in addition to a clear description of the testing protocol? Was the appropriate range of practitioners included in the testing?
7. Was the composition of the FMEA team appropriate with respect to the number of people, healthcare expertise, and medication error experience? Was the FMEA analysis thorough and well-structured (e.g., were all relevant failure modes and associated effects identified, did the analysis consider all potential practice use settings, were product characteristics beyond the proprietary name considered)?
8. If alternate or additional testing methods were used, were these well described and documented?

C. Increasing transparency

Although one objective of the pilot program is to increase transparency of the name evaluation and FDA review processes, in some cases FDA has access to information that is not publicly available to applicants. The FDA will communicate with the applicant to the extent permitted by law to describe the nature of this information. Some examples of situations where FDA may have information that influences its assessment but was not known to applicants include:

- Other names are in the review pipeline that, in the Agency's view, may cause confusion or possible medication error. Under FDA's regulations, information in an unapproved

application, including proposed proprietary names, is generally not publicly available (see 21 CFR §§ 312.130, 314.430, 601.50 & 601.51).

- FDA is aware of postmarket experience or error risks that the applicant may have overlooked or to which the applicant did not have access.

APPENDIX A: COMPUTERIZED RESOURCES

In most cases, the computerized resources listed here are publicly available.

Adverse Events Reporting System (AERS)

AERS is a database application in CDER that contains adverse event reports for approved drug products and therapeutic biologics. Manufacturers, for example, are required to send adverse event reports to FDA as specified in FDA regulations, and healthcare professionals and consumers are encouraged to voluntarily report possible errors to the FDA. The main utility of such a spontaneous reporting system is to identify potential postmarket safety issues. There are inherent limitations to this system, however. For example, there is underreporting and duplicate reporting; information received may be incomplete; for any given report, there is no certainty that the reported suspect product(s) caused the reported adverse event(s); and raw counts from AERS cannot be used to calculate incidence rates or estimates of drug risk for a particular product or used for comparing risk between products.

Vaccine Adverse Event Reporting System (VAERS)

VAERS is a cooperative program for vaccine safety of the Centers for Disease Control and Prevention (CDC) and FDA (CBER). VAERS is a postmarket safety surveillance program, collecting information about adverse events that occur after the administration of U.S. licensed vaccines. The VAERS Web site provides a nationwide mechanism by which adverse events following immunization can be reported, analyzed, and made available to the public. The VAERS Web site also provides a vehicle for disseminating vaccine safety-related information to parents/guardians, healthcare practitioners, vaccine manufacturers, state vaccine programs, and other constituencies. The majority of VAERS reports are sent in by vaccine manufacturers and healthcare practitioners. However, these data are subject to limitations such as underreporting, simultaneous administration of multiple vaccine antigens (making it difficult to know to which of the vaccines, if any, the event might be attributed), reporting bias, and lack of incidence rates in unvaccinated comparison groups. When evaluating data from VAERS, it is important to note that for any reported event, no cause and effect relationship has been established. The report of an adverse event to VAERS is not documentation that a vaccine caused the event.

Micromedex Integrated Index

This reference contains a variety of databases covering pharmacology, therapeutics, toxicology, and diagnostics. This information may be useful for naming because it contains a large number of product names marketed both domestically and abroad.

Phonological and Orthographic Computer Analysis (POCA)

This application was designed by the FDA. As part of the name similarity assessment, proposed names are evaluated via a phonological/orthographic algorithm. The proposed proprietary name is converted into its phonemic representation before it runs through the phonological algorithm. Likewise, an orthographic algorithm exists that operates in a similar fashion. The source code

and supporting technical documentation for this tool will be available for public use by the end of FY 2008.

Drug Facts and Comparisons, online version, St. Louis, MO

Drug Facts and Comparisons, a part of Wolters Kluwer Health, is a compendium developed for health professionals. The compendium is organized by therapeutic class; contains monographs on prescription and nonprescription products, with charts comparing similar products. (http://online.factsandcomparisons.com/index.aspx?)

Drugs@FDA

Drugs@FDA (http://www.accessdata.fda.gov/scripts/cder/drugsatfda/) is an FDA Web site that catalogs most of the drug products approved in the United States 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 information about FDA-approved brand name and generic drugs and therapeutic biological products prescription and over-the-counter human drugs and therapeutic biologicals, and discontinued drugs.

CBER Products

The CBER Products Web site catalogs most of the biologic products currently reviewed by CBER. Many of the labels, approval letters, reviews, and other information are available for products approved from 1996 to the present (http://www.fda.gov/cber/products.htm).

Electronic online version of the FDA Orange Book

This Web site provides a compilation of approved drug products with therapeutic equivalence evaluations (http://www.fda.gov/cder/ob/default.htm).

United States Patent and Trademark Office

This Web site provides information regarding marketed and pending patents and trademarks (http://www.uspto.gov).

Clinical Pharmacology Online

This resource, provided by Thomson & Thomson's SAEGIS ™ Online Service, contains full monographs for the most common drugs in clinical use, plus mini monographs covering investigational, less common, combination, nutraceutical and nutritional products. It provides a keyword search engine (www.thomson-thomson.com).

The Pharma In-Use Search Database

This database contains more than 400,000 unique pharmaceutical trademarks and trade names that are used in about 50 countries worldwide. The data are provided under license by IMS HEALTH.

Natural Medicines Comprehensive Databases

This Web site contains up-to-date clinical data on the natural medicines, herbal medicines, and dietary supplements used in the western world. (http://www.naturaldatabase.com)

Stat!Ref

STAT!Ref, is a subscription-based, online medical reference library that contains full-text information from approximately 30 texts, including tables and references. Among the database titles are: Handbook of Adverse Drug Interactions, Rudolph's Pediatrics, Basic Clinical Pharmacology and Dictionary of Medical Acronyms Abbreviations. (http://www.statref.com)

USAN Stems

The USAN Council (tri-sponsored by the American Medical Association (AMA), the United States Pharmacopeial Convention (USP), and the American Pharmacists Association (APhA), aims for global standardization and unification of drug nomenclature and related rules to ensure that drug information is communicated accurately and unambiguously, working closely with the International Nonproprietary Name (INN) Programme of the World Health Organization (WHO), and various national nomenclature groups. This Web site, managed by the AMA, contains lists of all of the recognized USAN stems.
(http://www.ama-assn.org/ama/pub/category/4782.html)

Red Book Pharmacy's Fundamental Reference

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

Medical Abbreviations Book

Various references on this topic are available. These references contain commonly-used medical abbreviations and their definitions.

APPENDIX B: PROPOSED TEMPLATE FOR A PILOT PROGRAM SUBMISSION

I. Table of Contents

II. Executive Summary

Provide a summary of the overall findings of the proprietary name review including the rationale as to why the name is acceptable.

III. Introduction

a. Identify the primary and alternate proprietary name(s).

b. Provide information to support the FDA's traditional name review[19] and/or provide the container label, carton labeling, and professional insert in an Appendix.

IV. Safety Review

a. Preliminary Screening

Describe the methods used and considerations given to the proprietary name in the prescreening process. If a proposed name fails the preliminary screening and is submitted to the FDA for evaluation, describe the rational for pursuing the name.

b. USAN Stem Search

Include a statement that indicates the name(s) does not contain a USAN stem along with the date on which this information was searched on the USAN list.

c. Orthographic and Phonological Similarities

Provide the following information: .

- All search queries
- The system parameters used for each search (e.g., letter substitution)
- The precise databases searched
- Any thresholds imposed on the output (e.g., top 100, top 200, etc.)
- The date the search was conducted or the last update of the database that was searched
- Pooled results with source citation and full product characteristics of each name identified as a possible source of confusion with the proposed name.

[19] FDA is developing guidance on the content of a complete submission for the evaluation of proprietary names.

Note: Although such searches generate many names that may be ruled out under further analysis, we request that all names initially identified as a potential source of confusion be submitted.

d. Computational Methods

Provide the following information on the computational method(s) used:

- The measure of similarity/distance used
- The values assigned to any adjustable parameters
- The manner in which non-name attributes (e.g., strength, dosage form, route of administration) were handled
- If a weighting scheme was used, describe how the different elements were weighted
- The precise database searched (e.g., Orange Book, including or excluding discontinued products, USPTO (what class), Multum Lexicon).
- If a cutoff or threshold was used to narrow or widen the search results, the cutoff or threshold, and how and why it was chosen
- Testing output

e. Medication Error Data

If your proposed product contains an active ingredient that is marketed domestically or abroad, all available information relevant to medication error cases associated with that active ingredient should be identified and submitted to the FDA. Relevant information would include any error reports related to the product nomenclature, active ingredient, package, and/or the label and labeling. This information should be identified and reported to the FDA in line listings with a narrative as described in the box below.

Format for Submitting Relevant Information

- The FDA recommends that applicants submit a line listing and narratives of the medication error case reports identified in the postmarket period for marketed products with the same active ingredient as the product under review.
- The applicant should cite the source of the report along with any analysis conducted by the applicant. Applicants should submit the full text of any article published on medication errors associated with the product.
- Applicants should also categorize these errors by type (e.g., incorrect product, incorrect route of administration) using the NCC MERP taxonomy.
- Applicants should review these cases to identify factors that contributed to the medication errors and to ascertain whether these risks apply to the proposed proprietary product name. All medication error data should be integrated into the FMEA.

f. Name Simulation Studies

Describe all methodology associated with the simulation study including but not limited to how participants were chosen and the composition and qualifications of participants.

g. Failure Mode and Effects Analysis

Provide the relevant information to demonstrate that the name will not lead to confusion. Describe the methods associated with the FMEA (how the team was chosen, the composition of the team, qualification of its members, the failure modes identified, and any proposed risk mitigation strategies).

V. Promotional Review (if applicant chooses to participate in this aspect of pilot)

Describe all research methodology used to support a proposed proprietary name, including a description of participant demographics; the product profile provided to the study participants; the complete survey questionnaire; the coding scheme used to analyze open-ended questions; complete results (both positive and negative), including results of pretests; and any other information given to the study participants regarding the drug approval process and the regulations regarding proprietary names.

VI. Alternative Methods

If the methods used to assess the proposed proprietary name differ from those suggested in the concept paper for the PDUFA Pilot Project - Proprietary Name Review, submit the rationale for deviation, a full description of the methods, and all data generated and any analysis of this data from the alternative test method(s).