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A Method of Addressing Proprietary Name Similarity for US Prescription Drugs

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Abstract

There is an increased risk of medication error and harm to a patient whenever 2 or more drug product names appear alike in sound, look, or meaning. Any ambiguity of the proprietary name ("trade" or "brand" name) of a drug product can lead to errors in ordering, dispensing, or administering medication. A drug's name is a critical identifier, and correct product identification is important to the responsible administration of medicine. This article describes a series of tools created for regulatory reviewers to enhance the review of proprietary names under current federal regulations, with the goal of encouraging further innovation toward the goal of medication safety. These tools include measures of orthographic, phonetic, and semantic similarities and are designed be used together with the existing computerized measures of similarity. It is the hope that highlighting the importance of medication error reporting for the safety review process will further encourage health care professionals to provide adequate and detailed reporting regarding medication errors, which will lead to improvements in the overall safety review process.

Keywords

medication error, error review, prescription, brand name, trade name

There is an increased risk of medication error and harm to the patient when 2 or more product names appear alike in sound, look, or meaning.[1,2] A proprietary name ("trade" or "brand" name) communicates the product intended for administration to the patient. Any ambiguity or misinterpretation of the proprietary name can lead to errors in ordering and dispensing (eg, confusing one product name for another) or administering medication (eg, wrong dose or wrong frequency).[2] Since a product's name is the critical identifier of the appropriate therapy in a market of thousands of products, accurate interpretation of the proprietary name is important to the responsible administration of medicine.

In 2000, the Institute of Medicine (IOM) published a report titled *To Err Is Human: Building a Safer Health System* citing medication errors as a public health concern that accounts for thousands of deaths annually in the United States.[3,4] The report recommended that Food and Drug Administration (FDA) require pharmaceutical companies to test proposed proprietary names to identify and remedy potential sound-alike and look-alike confusion with existing drug names. On September 27, 2007, the reauthorization and expansion of the Prescription Drug User Fee Act (PDUFA IV) was signed into law as part of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law 110-85). As part of the PDUFA IV reauthorization, FDA committed to certain performance goals, including measures to reduce medication errors related to look-alike and sound-alike proprietary names, unclear label abbreviations, acronyms, dose designations, and error-prone labeling and packaging designs.[i] To address this commitment, the FDA Center for Biologics Evaluation and Research (CBER) and Center for Drug Evaluation and Research (CDER) have worked to develop a systematic, standardized approach that provides increased transparency within the proprietary name review process.

The Federal Food, Drug, and Cosmetic (FFD&C) Act Section 201 and 21 U.S.C. 321 (n) provide authority for the Food and Drug Administration to address issues of misbranding, as related to misleading representations (statements, words, and design) in labeling or advertising, to the extent to which there is a failure to reveal material facts in light of such

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representations. Proprietary name reviews are further divided into 2 distinct tracks of consideration for misleading content: fanciful promotional content (21 CFR 201.10(c)(3)) and name similarity that increases the risk of potential medication error (21 CFR 201.10(c)(5)). Specifically, 21 CFR 201.10(c)(3) states that a product may be misleading if it has a fanciful name, implying that the product or ingredient has some unique effectiveness or composition when it does not (eg, *Miraculo*). In addition, 21 CFR 201.10(c)(5) states that a product may be misleading if the proprietary name, because of similarity in spelling or pronunciation, may be confused with another proprietary or established name. Written guidance has been developed for industry sponsors regarding their submissions of proposed proprietary names. These guidance documents provide best practice recommendations strongly encouraged for developing proprietary names based on the regulations and processes used by reviewers currently.[5,6] These recommendations apply to *all* human prescription and nonprescription drug products, including biological products. This article describes a computer module of tools that was created for regulatory reviewers to enhance the consistency of the review of proprietary names, as it relates to regulation under 21 CFR 201.10(c)(3) and 21 CFR 201.10(c)(5), with the goal of encouraging further innovation and improvement toward a common goal of medication safety.

The Proprietary Name Review Process

Proposed proprietary names under review by the FDA are compared to the existing corpus of proprietary and established names for prescription and over-the-counter drug products. Proprietary names for drugs and biological products almost always are neologisms, or new words, inserted into the English language for use in the health care setting. The strategic creation of a neologism used for a proprietary name is far from an arbitrary process; it is wrought with influence from existing languages. This may include following the rules of permissible sound ordering found in a given language (phonotactic rules), allowing the neologism to be intuitively pronounced by speakers of that language. It also may include allusion to existing words in a given language via word segments of various sizes or, less commonly, using new spellings of existing words. Promotional review seeks to interpret semantic content (or ''meaning'') conveyed in the proprietary name that primarily is imparted by these influences. In a sense, this can be thought of as ''reverse engineering'' the process used to make the proprietary name neologism.

Consideration of a proposed proprietary name for risk of name-related medication error can be divided further into 3 separate subcategories, representing potential causes of confusion: names that sound similar (''sound-alike'' or phonological similarity), names that appear similar when written either in printed or scripted text (''look-alike'' or orthographic similarity), and names that bring to mind the same general ideas or concepts (''content-alike'' or morphological or semantic similarity). Consider the following errors resulting from confusion of similar drug names: Lamictal and Lamisil, Cerebyx and Celebryx, Serzone and Seroquel, Avandia and Coumadin. Confusion between these similarly named drug pairs has been reported and has caused serious adverse events. The existing proprietary name review process strives to address each of these factors effectively and conservatively, accounting for use environment, mode of delivery, and other aspects of the product conveyance when determining the risk for potential medication error.

The proprietary name review process follows discrete, transparent steps to facilitate consistent reviews from a given reviewer as well as across reviewers and FDA centers. The steps, as follows, are developed to target those proposed proprietary names that are most likely to cause phonetic, orthographic, and semantic similarity resulting in possible error:

1. Identify names with potential similarities in how they are pronounced (sound-alike), spelled, or appear when written in print or script (look-alike).
2. Simulate names.
3. Review medication error data.
4. Conduct a contextual analysis of product use.

Validating the effectiveness of this process often is pursued through review of actual medication error data, as provided through spontaneous reporting. Certain errors attributed to sound-alike and look-alike similarities are predictable.[7] The paucity of reported medication errors and the difficulty of post hoc ascription of an error to a phonetic, orthographic, or semantic similarity make assessment of the effectiveness of any review practice difficult. Thus, it is hoped that highlighting the importance of this safety review process will encourage the health care community and consumers to report medication errors, as they occur, with as much detail as possible.

Step 1. Identify Names With Similarities to the Proposed Proprietary Name

A computer module of tools was created for regulatory reviewers to structure the process of identifying and assessing name similarity in sound, look, and meaning. The tools provide a comprehensive, open resource and a common ground of knowledge and terminology with which to discuss the various types of similarity and the evidentiary basis for a claim of potential for medication error.

Complete an Overview

Reviewers begin the proprietary name review process by gathering general, holistic information about the product under

review. This information includes the established name, the product description, and the intended use environment. It also may include a brief subjective consideration of what the name sounds like, intuitively, from the perspective of a natural language user. Many times this information can be elucidating to the nature of the name and the import one may predict.

Examine the Morphological Import of the Neologism

Reviewers support their intuitive consideration through an objective review of the morphological and semantic associations in the neologism, those that directly build meaning into the new word.[8] Morphemes are the smallest structural units of language broadly accepted to carry discrete meaning (eg, *apple* is a morpheme, but *apple*s has 2 morphemes, as the *-s* is a sound that carries the meaning of "more than one"). Language users continually manipulate language in terms of morphemes in order to inflect words appropriately and express the content that they hope to communicate (eg, *un-happy-ed* is not a word, but using the parts of words native speakers are familiar with, a speaker could guess at the intended meaning of the speaker). In the proprietary name review process, reviewers consult an aggregated list of morphemes and word roots (not only words), containing both general common morphemes in English usage and specialized "lexicon," or vocabulary more specialized and common to the medical context.[9,10] The list includes actions (*vert*: turn, change; eg, *convert*), adjectives (*juven*: young; eg, *juvenile*), and specific corpora relating to body parts (*gloss*: tongue; eg, *glossary*), frequency (*dec*: ten; eg, *decimate*), life (*viv*: life; eg, *vivid*), nature (*aqu*: water; eg, *aqueous*), negation (*un*: not; eg, *unceasing*), novelty, number, order, people, pejoration, proximity, safety, and color. In addition, reviewers consult the United States Adopted Names stem list,[11] as this is a resource commonly used by branding agencies in the pharmaceutical industry. Not every morpheme or root that can be said to appear in the new word is intentional. The reviewer attempts to harmonize the potential meaning of information embedded in the name with the known product information in order to come up with a conceptualization of the intended meaning of the neologism.

Examine the Phonesthemes and Phonosemantic Import of the Neologism

In addition to the more commonly cited morphological level of meaning, many neologisms are perfected using a more nebulous consideration of the influence of the individual phonemes on the perception and interpretation of the word, either meaningfully (phonesthemes) or symbolically (phonosemantics). Phonesthemes are sets of sounds that allude to meaning carried in morphemes. For example, /gl/ could allude to light (eg, *gleam*, *glow*) or smoothness (eg, *glide*, *glacier*).[12,13] In contrast, there is a classically cited example of phonosemantics in which the significant observed effect is that, if presented with a rounded cloud-like shape and a spikey hard-lined shape and then asked which shape is associated with potential labels such as *bouba* and *kiki*, most people will associate *bouba* with the rounded shape and *kiki* with the spikey shape.[14-16] The import of sound symbolism often is sufficiently convergent to influence language interpretation; those who design names can rely on consistent effects of certain sounds on the impressions that the listener will have about the new word. The meaningful import of phonemes is neither discrete nor literal, but can be powerful in the interpretation of an unfamiliar word. Two common sound and concept correspondences include sounds made with round lip position being associated with rounded objects and femininity and sounds made with narrow or angular lip positions being associated with angular or masculinity. Qualities such as speed, size, dependability, and salience of memory recall may be manipulated at this level. For example, voiceless sounds produced with a puff of air, such as /p/ and /k/, are associated with more speed than similar voiced sounds /b/ and /g/, but less speed than sound produced using a steady stream of air disrupted by the mouth's articulators, such as /f/ and /z/. As with the morphological affixes, aggregated data on these relationships are used to "decode" their import to proprietary names.

After determining the meaning or content and sound-carried impressions of a neologism, reviewers examine the proposed proprietary name for content-alike traits and general congruency. For example, when multiple products reference content associated with youth (eg, *juven*, *pedia*, *infa*, *neo*), it is first established that the product name using or alluding to these forms is actually a product intended for use in pediatric populations. This semantic congruency is necessary, as it is likely to be inferred from the product name. Further, if different product names are similar but for the presence of different morphemes with the same meaningful import, this may be cause for concern that the names could be confused, resulting in name-related medication error. In some cases, interchange may be acceptable or desirable. This is determined on a case-by-case basis.

Dissect and Analyze the Phonetic Content of the Neologism

Broad citation style transcription using the International Phonetic Alphabet is used to denote the speech sounds (phonemes) present in the proposed proprietary name.[17] This specialized alphabet represents the way words are pronounced instead of their classic spelling, much like music notes represent the way a song is played. While many pharmaceutical companies may suggest their intended pronunciation of the neologism, this interpretation is not relied on to the exclusion of other intuitive pronunciations of the proprietary name as it is written. Typically, reasonable pronunciations of a given neologism are

addressed exhaustively, accounting for a diversity of regional, social, and ethnic variations of English. Next, a series of processes are applied to the citation form transcription to account for potential effects of sound context on the pronunciation of the speech sounds in the proposed name. These processes are chosen to mimic the most statistically common effects of rapid continuous speech on speech sounds (eg, weak syllable lenition, feature assimilation, and vowel centralization). Changes are made systematically to retain the most salient phonological features of the neologism as occurs in typical connected speech. Throughout this process, reviewers focus on the overall likelihood of the output form and avoid considering iterations that are so far afield of the intended proprietary name as to be unrecognizable. The result is a transition from examining a single neologism presented in English spelling (orthography) to a discrete set of likely potential pronunciations and variations presented in an alphabet with one-to-one sound spelling correspondence. A classic example of sound-alike similarity resulting in confusion is the similarity between the names Kapidex and Casodex (Kapidex has since been rebranded to a different name to minimize this risk).

Reanalyze the Orthography of the Neologism

At this point in the review, reviewers translate the set of phonological representations back into discrete English spelling, such that it can be used to search for similar proprietary and established names. This is done using a tool that lists all possible spellings of each English sound. While these correspondences are much more divergent, there are discrete sets of letters associated with each sound in the English language. The tool includes spellings that are very common as well as atypical spellings or those that only occur in a certain place in a word (eg, *gh* can be used to represent the /f/ sound, but only in word-final position, *enough*). Reviewers then examine this information for the most common spellings to avoid unnecessary diversity. The final result is a discrete set of terms that can be used to search for sound-alike names within existing databases as well as a basis for the look-alike (orthographic) review of the name.

Orthographic review is done on 2 levels: the whole word level and the individual letter/letter cluster level. Whole word orthographic similarity can occur when 2 words have a similar overall outline or shape (eg, *Organ* and *Gaper*) and is determined based on heights of letters (''x-height lengths'') and letter shapes within the word.[8] A classic example of error resulting from orthographic similarity is the similarity of Avandia and Coumadin, particularly when the 2 names are written in scripted text. Letter cluster orthographic similarity occurs when 2 or more letters together are very similar in appearance to a single other letter (eg, *d* and *ol*).

To create the orthographic tool for the module, common similarities across letters and letter clusters were established using a connected pangram, written by a set of participants in lower- and upper-case print and cursive. These letters were then individually considered with respect to one another to establish highly common ambiguities within and across writing styles. When scripting a proprietary name, individual letters or letter strings may look different than those that are printed. The data were analyzed and trends were identified. Some examples include

- ''T'' may look like ''F''
- ''a'' may look like ''u''
- a scripted capital ''A'' may look like ''C,'' ''Ci,'' or ''Cl''
- ''en'' may look like ''ar,'' ''in,'' or ''ea''
- ''cl'' may look like ''d''
- ''oti'' may look like ''ali''

While the orthographic review is included in the proposed proprietary name review process, its outcomes only are considered as additional evidence of a potential name ambiguity, not as necessary or sufficient evidence of ambiguity alone. This is in consideration of the extremely high variability in writing styles and legibility.

Search Databases of the Existing Proprietary and Established Names

The possible spellings associated with a discrete, probable diversity of pronunciations constitute a set that may be entered into any of a number of relevant query tools, including but not limited to the Phonetic Orthographic Computer Analysis (POCA) database recently designed.[18] POCA was developed specifically for the examination of phonetic and orthographic similarities. The queries assign a similarity score to a given word. POCA search results evidencing potential similarity above 70% are very concerning and are likely to be viewed as problematic from a safety perspective. Those between 50% and 70% are considered potentially problematic, depending on other contextual factors that may increase or mitigate a potential for medication error, such as differences in strength or dose.

Step 2. Conduct Name Simulation Testing

Name simulation tests the response to a proposed name by using the name in simulated real-world conditions. This method provides a high standard of ecological validity for the proprietary name review process. 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 (eg, use of lined paper, prescription pads, different handwriting samples, different color inks, telephone ''orders'' with different

voices/accents, and background noise). Name simulation is conducted via survey of participating internal FDA employees (health care professionals and consumers). Responses are recorded and are used to inform the evaluation of the potential for confusion of a proposed name. Most importantly, name simulation may uncover additional names of concern not otherwise identified through the more formulaically structured methods described previously.

Step 3. Analyze Medication Error Data

Data obtained from case reports of medication error inform the analysis of a proposed proprietary name and overall product design. The FDA searches its post-marketing surveillance system (MedWatch; www.fda.gov/Safety/MedWatch/default.htm) and US vaccine adverse event reporting system (VAERS; www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/ReportaProblem/VaccineAdverseEvents/Overview/default.htm) databases to look for medication error reports, and it analyzes the failures that contributed to the medication error(s). Relevant information may include any error reporting related to the proposed proprietary name, product design, label, and labeling.[ii] As stated previously, this review may be of limited value because of the overall dearth of reported medication errors, the lack of detail in many of the reports, and the difficulty in ascribing a particular error to a phonetic, orthographic, or semantic similarity.

Step 4. Conduct a Contextual Analysis of Product Use

After determining names that may cause potential medication errors due to phonetic or orthographic similarities, the context of use that may increase or mitigate the potential for a medication error is examined. Here, the vulnerabilities of the name are examined. Product profile characteristics (eg, indication, dose, dosage form, strength[s], and route of administration), storage, patient population, and health care environment are all considered in this analysis. The health care context and environment even may include proprietary names and established names that are highly prevalent in other countries, acknowledging the potential for international exchange to result in name-related medication errors. The nature of a potential medication error also is considered. Post-market experience has shown that similarity in nomenclature, as well as the design of the container label, carton labeling, and packaging of a product, directly contribute to the occurrence and the likelihood of medication errors. In some cases, name pairs have been identified that share multiple dimensions of similarity; for example, sharing the related—though distinct—sound, spelling, and orthographic similarity at the same time. Classic examples of such pairs include Lamictal and Lamisil or Cerebyx and Celebrex. In these cases, all modes of communication of the name within the health care environment have shown risk for name confusion. There are predictable and preventable types of medication errors that can be mitigated prior to approval, when actions to overcome these issues are easier to implement than remedies available in the post-approval phase.

Conclusion

Proprietary name confusion is considered a preventable event and a risk that can be mitigated with the use of an alternative name. The process described here reflects 2 major goals benefiting both pharmaceutical safety regulation and innovation by industry: (1) to identify proposed proprietary names that are likely to cause phonetic (sound-alike), orthographic (look-alike), or semantic (content-alike) similarity resulting in error while minimizing the identification of superfluous names, thus rendering the proprietary name review process both effective and efficient; and (2) to put forth a process that is sufficiently objective and transparent in order to produce consistent, predictable results from reviewers knowledgeable in using the tools appropriately. The production of convergent, consistent reviews of proprietary names requires the reviews themselves to be regularly examined for consistency. In this way, the regulatory offices can strive to provide an objective and consistent application of the promotional and safety review procedures.

Computerized methods are useful in developing a list of possible names that may be confused with the name under review; however, they are not used for the more complex task of evaluating which names have potential for error. No single method can ever evaluate all dimensions of similarity, nor will any single measure perform as well as an intelligently assembled combination of measures (eg, one that integrates measures of orthographic, phonetic and semantic similarities). Predictions based on computerized measures of similarity will occasionally yield both false positive predictions (ie, saying a pair is confusing when it is not) and false negative predictions (ie, saying a pair is not confusing when it really is). The importance of the contextual analysis should not be underestimated.

It is the hope that highlighting the importance of medication error reporting for the safety review process will further encourage health care professionals to provide adequate and detailed reporting regarding medication errors, which will lead to improvements in the overall safety review process.

Notes

i. See letters 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 (goals letter). Available at http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm119243.htm.

ii. See 21 CFR 312.32(b). Current regulations require applicants, when filing an application, to submit a review of all information relevant to the safety of the product from any source, foreign or domestic, including information derived from clinical or epidemiological investigations, commercial marketing experience, reports in the scientific literature, unpublished scientific papers, and reports from foreign regulatory authorities.

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