Designing Safe Drug Names

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Abstract

Recent observational studies of medication errors in community pharmacies suggest that "wrong drug" errors, which occur when a patient receives a drug other than what was prescribed, may occur as many as 3.9 million times per year in the U.S. Similarity between drug product attributes, especially similarity between drug names, is thought to be a contributing cause of these errors. The challenge facing drug companies is to design new drug names that will not be confused with existing names. In this essay, we attempt to lay out a systematic approach to the design of safe drug names. We begin by providing some basic facts about drugs names. We proceed to characterize the process of design as a multiple-objective optimization problem. We then identify and define the most important constraints and objectives that a drug name must satisfy. Next we discuss and critique methods for evaluating a given name with respect to each safety objective and constraint. Finally, since no single design will be optimal with respect to all of the objectives, we describe several approaches to selecting one design from a set of competing alternatives. The pharmaceutical industry and the U. S. Food and Drug Administration have taken important steps recently to improve the pre-approval screening of new drug names, but a great deal of research still needs to be done to establish a valid scientific basis for these decisions.

Key words: drug names, medication errors, multiple criteria decision making

Introduction

Confusions between drug names that look and sound alike (e.g., *Keppra*® and *Kaletra*®, *Indocid*® and *Endocet*®)[4] continue to occur frequently, and each confusion poses a threat to patient safety.[5-9] A recent national observational study of dispensing errors in U.S. outpatient pharmacies reported that the "wrong drug" error rate was 0.13% (6 out of 4481 prescriptions observed in 50 pharmacies).[10] Wrong drug errors are also the most common source of malpractice claims against pharmacists.[11] Not every wrong drug error is the result of a name confusion, so this figure should be seen as an upper bound on the rate of name confusions that occur in outpatient pharmacy. At first this might appear to be good news. It means 99.87% of the time, patients get the right drug, but with about 3 billion prescriptions filled by outpatient pharmacies each year in the U.S.,[12, 13] the 0.13% error rate results in *3.9 million* wrong drug errors per year. If 6.5% of those errors are clinically significant, as Flynn et al. report, then 253,500 clinically significant wrong drug errors occur each year in outpatient pharmacies (695 per day). Assuming there are 55,000 community (outpatient) pharmacies in the U.S.,[12] one clinically significant wrong drug error occurs every 80 days in every single outpatient pharmacy in the U.S. The purpose of this article is to examine how this problem might be addressed by continuing to integrate safety concerns into the design of new drug names.

Preventing drug name confusions involves both pre-approval and post-approval strategies. Pre-approval strategies ensure that confusing *new* drug names do not enter the marketplace. There are a variety of pre-approval tests that can be done on a name to test its vulnerability to confusion. These include computerized searches for existing similar names or products,[14] soliciting expert judgments about confusability,[15] doing traditional psycholinguistic

tests on memory and perception,[16-18] and observing error rates during simulated ordering, dispensing, and administration tasks.[1, 3]

A different set of strategies is needed to prevent confusions between confusingly similar names that are *already in use*. Preventing confusion between already marketed products typically involves collecting voluntary reports of names involved in confusion errors, posting warnings and alerts both electronically and in areas where drugs are used, including the indication on the prescription, storing confusing drugs in different locations, improving lighting, providing magnifiers, removing one of the confusing drugs from the system, or insisting on double-checking for products thought to be vulnerable to confusion.[19]

Overview

In this article, we focus on pre-approval strategies for preventing confusion. In doing so, we attempt to lay out a systematic approach to the design of safe drug names. We begin by providing some basic facts about drugs names. We proceed to characterize the process of design as a multiple-objective optimization problem. We then identify and define the most important constraints and objectives that a drug name must satisfy. Next we discuss methods for evaluating a given name with respect to each objective and constraint. Finally, since no single design will be optimal with respect to all of the objectives, we describe several approaches to selecting one design from a set of competing alternatives. The article is based primarily on drug naming in the U.S., although an effort has been made to give international examples where appropriate.

Basic Facts About Drug Names

Drug nomenclature is complicated, in part because each drug product has many names. Proprietary, or brand names, such as *Viagra*®, are valuable intellectual property, coined by specialized consultants, owned by the manufacturer of the product and registered globally as

trademarks. Non-proprietary, or generic names, such as *sildenafil citrate* (the generic name for *Viagra*®), are assigned by regulatory agencies such as the United States Adopted Names (USAN) Council in accordance with strict rules.[20] Each drug may also have a chemical name, an established name, a common name, a trivial name, and one or more abbreviations.[21] The mere existence of multiple systems of nomenclature can sometimes be the source of confusion.[22, 23] Because of their familiarity and high profile, and because of the large investment required for their development, brand names tend to get the most attention.[6] Most of our focus here will be on brand names, although our overall approach to designing safe names would apply equally to generic names (and to device names, names of dosage forms, etc.).

How Many Drug Names Are There?

We reported previously[24] that there were 21,687 unique one-word names in the pharmaceutical category (i.e., international category 5) of the U.S. Patent and Trademark Office's database of registered trademarks[25] and 5331 unique generic names in the USP Dictionary.[20] However, many trademarks in international category 5[26] of the USPTO database refer to products other than drugs. Hence, 21,687 is a significant overstatement of the number of proprietary drug names in use in the U.S. We recently examined five different sources of prescribing frequency data: (a) the National Ambulatory Medical Care Survey (NAMCS)[27], (b) the National Hospital Ambulatory Medical Care Survey (HAMCS)[28], (c) the IMS National Prescription Audit Plus (NPAP)[29], (d) the Solucient• outpatient frequency database, and (e) the Solucient hospital drug utilization database.[30] These data suggest that there are no more than 11,000 drug names currently in use in the U.S., and no more than 4400 one-word names. In a related study, we combined the names from the FDA's Orange Book[31] and from the Multum

• Some data for use in this study were supplied by Solucient, LLC, Evanston, Illinois. Any analysis, interpretation, or conclusion based on these data is solely that of the authors, and Solucient disclaims responsibility for any such analysis, interpretation or conclusion.

Lexicon.[32] After removing generic names and duplicates, there were 5232 unique brand names remaining, of which 3681 were available only by prescription and 1551 were available over-the-counter. Due to inconsistencies in drug nomenclature and problems in automatic processing of the names, these should be regarded as estimates rather than definitive counts.

Design as a Process of Multiple Objective Optimization

In order to understand the design of drug names, it will be useful to have in mind an abstract model of the design process. Design involves the selection of a *feasible* point in *decision space* that simultaneously optimizes a given set of *objectives*. Formally, the designer selects a point in a multidimensional decision space that maximizes (or minimizes) a set of objective functions subject to a set of feasibility constraints. Detailed mathematical treatments of this subject are available in the literature.[33-35] Each of these terms will be discussed in turn.

Decision space. A design is a point in a multidimensional *decision space*. The dimensions of this space correspond to all of the possible parameters of the design. In the context of drug naming, the decision variables include the number of letters or phonemes, the number of syllables, and, most importantly, the identity of the letter or phoneme occupying each sequential position in the name.

Constraints. Not every point in the decision space is *feasible*. Feasible designs are only those which meet all of the *constraints* on a particular problem. Constraints describe boundaries or conditions that designs must not violate. Drug names are subject to a large and complex set of constraints. Some constraints, like pronounceability, are intrinsic to the problem. It makes no sense to have a drug name no one can pronounce. Others, such as the need to avoid names that are identical to existing names, the need to avoid a name that suggests an unapproved use, the need to use specific word stems in generic names, or the prohibition against using part of the

generic name in the brand name, reflect legal and regulatory requirements.[20, 21, 36, 37] Constraints are closely related to objectives (see below). Constraints can be thought of as inflexible objectives—design criteria that, for reasons of safety, efficiency, liability, etc., cannot be compromised. Although a designer hopes to optimize each objective, deviations from optimality are tolerated and even expected. In contrast, a constraint specifies a fixed condition that all acceptable designs *must* satisfy.

Objectives. Design objectives (or criteria) are the goals for the design, the qualities that the designer wants to maximize (e.g., memorability) or minimize (e.g., confusability). They are the dimensions along which each design will be evaluated. For example, a drug name designer might evaluate each design with respect to length, pronounceability, memorability, confusability, and so on. In most modern approaches, designers strive to define objectives in ways that can be reliably and validly quantified. If a design's score on each objective dimension can be quantified, then powerful mathematical tools can be used to search the space of possible designs for point that optimizes all of the objectives.[33, 34] Some objectives can be easily quantified (e.g., length), and some are more difficult (e.g., aesthetics, meaning).

What makes good design difficult is that different design objectives trade off against one another. Long drug names are more likely to be distinctive but will also be harder to remember. Very novel spellings may be highly memorable but difficult to pronounce. Memorable and easily pronounced names may be too similar to existing names. Names with the most desirable connotations may run afoul of regulatory constraints. Recognizing that no design will simultaneously maximize all design objectives, designers instead search for a set of points in decision space that maximize as many objectives as possible, within certain constraints.

The Decision/Design Space

Since the modal U.S. brand name has 8 letters,[24] the decision space includes at least eight variables corresponding to the 8 possible letter positions. If one considers only alphabetic characters and ignores case, each position has 26 possible values. Thus, this part of the design space consists of 26^8 or roughly 209 billion possible letter strings. One might think that the situation would be simplified by designing in terms of sounds rather than letters. But there are 28 consonantal sounds and 20 vowel sounds in English.[38] If we assume 8 possible sequential positions for these phonemes, the designer is still faced with 48^8 (28 trillion) possible sequences. In theory then, it does not seem likely that space for distinctive new names is running out. But there is more to the story than just the theoretical capacity of the name space. The space of *feasible* names (i.e., names that satisfy all relevant constraints) is much smaller than what has just been described (although still very large).

Constraints on Drug Names

Practical constraints. Constraints on drug names fall into two categories: practical and legal/regulatory. The primary practical constraint is pronounceability. The selected letter string must be pronounceable, that is, it must be a legal string in English. "*Otjxkzz*" might be a highly distinctive and memorable letter string, but it is useless as a brand name because it is impossible to pronounce, and it includes letter sequences that do not occur in ordinary English words. The set of pronounceable names represents only a small proportion of the total set of theoretically possible strings because many sequences of letters or phonemes do not occur in English.[38-41] So the feasible decision space is much smaller than the whole decision space.

To our knowledge, no one has quantified what proportion of possible strings would result in pronounceable words. This is an important topic for future research because it directly

addresses the capacity of the name space and the extent to which space for non-confusing new names might be "running out." Theoretically, the capacity of the name space is defined as the number of pronounceable words that could be generated for a given word length (e.g., 8 characters) and a given alphabet (e.g., the 26 letters of the English alphabet). One could take the total number of existing 8-letter drug names, divide by the total capacity, and arrive at a rough estimate of how close the name space is to full capacity.

Legal and regulatory constraints: U.S. Legal and regulatory constraints are numerous, and they differ for brand versus generic names.[21] For generic names, the constraints are spelled out in a ten page appendix to the USAN Handbook entitled "Guiding Principles for Coining United States Adopted Names for Drugs."[42] Several of USAN's specific rules can be viewed as constraints. For example, the strings "th", "ph", and "ae" are prohibited and should be replaced by "t", "f", and "e" respectively.[42] Isolated numbers, letters, and hyphenations should be avoided.[42] In addition, "prefixes that imply 'better,' 'newer,' or 'more effective,' or evoke the name of the manufacturer, dosage form, duration of action or rate of drug release or have an anatomical connotation are unacceptable."[42] In all, there are 8 general rules (which function more as objectives than as constraints) and 16 specific rules. Names must also incorporate USAN stems to capture similarities in pharmacologic categories, mechanisms of action, or chemical structure. The interested reader should consult the USAN Handbook for additional details.[42]

For brand names, there are also a host of legal and regulatory constraints. Some legal constraints arise out of state and federal trademark law (i.e., the Lanham Act) and from rules and regulations enforced by the U. S. Patent and Trademark Office.[43] It is beyond the scope of this article to delve into the details of trademark law, but good references are available to those who

are interested.[44] In the U.S., regulatory constraints on drug names are primarily enforced by the U. S. Food and Drug Administration, whose authority derives from federal law.[45] Boring has provided a good summary of the issues.[21] Federal law prohibits "misleading" drug names. The following sections of the federal statute are most relevant to the discussion of constraints:

> 21CFR201.10(c)(3) The employment of a fanciful proprietary name for a drug or ingredient in such a manner as to imply that the drug or ingredient has some unique effectiveness or composition when, in fact, the drug or ingredient is a common substance, the limitations of which are readily recognized when the drug or ingredient is listed by its established name.
>
> 21CFR201.10(c)(4) The featuring in the labeling of inert or inactive ingredients in a manner that creates an impression of value greater than their true functional role in the formulation.
>
> 21CFR201.10(c)(5) Designation of a drug or ingredient by a proprietary name that, because of similarity in spelling or pronunciation, may be confused with the proprietary name or the established name of a different drug or ingredient.[45]

To the extent that these regulations represent categorical prohibitions, they will function as constraints. Those that are more flexible and open to interpretation will function more like objectives.

Legal and regulatory constraints outside the U.S. International legal constraints on drug names resemble those in the U.S. These issues were summarized in a recent report by Health Canada.[46] The European Agency for the Evaluation of Medicinal Products (EMEA), which regulates drugs in the European Union (EU), ensures that "a medicinal product should not bear an invented name potentially to be confused with that borne by another medicinal

product."[47] In evaluating new names, the EMEA strives to implement a "transparent procedure" based on "consistent non-arbitrary criteria" of acceptability.[47] Acceptable names should not convey misleading connotations about therapeutic value or chemical composition and should not be "liable to cause confusion in print, handwriting or speech" with existing names. Differences in dosage form, route of administration, indication and legal status of the product should be considered as mitigating factors if two names are thought to be similar. In all cases, potential safety risk is said to be the "paramount criterion". In addition to the non-confusability constraints, invented (i.e., brand) names should not be derived from USAN or International Nonproprietary names, should preferably consist of only one word, should avoid non-standard suffixes, and should not convey promotional messages.[47] Outside the EU, according the Health Canada summary, New Zealand enforces a basic non-confusability constraint. Japanese and Australian regulators are attuned to the issue but do not yet have detailed policies or procedures in place.[46]

Objectives in the Design of Drug Names

USAN Objectives. According to the USAN Council, generic names must be useful, simple, euphonious (i.e., pleasant sounding), and easy to recall, recognize, and pronounce. USAN names should be single words, perhaps with additional one-word modifiers.[42]

Confusability. Generic names should be free from conflict with existing names and "neither confusing nor chemically misleading."[42] As stated above, the FDA also enforces a prohibition against confusing brand names. In both cases, confusability can function as both a constraint and an objective. It is a constraint in the sense that, when a name is deemed by the FDA to be confusing, it is rejected and it may not be used to market a drug product in the U.S. Roughly one third of all names evaluated by the FDA are rejected for this reason.[1, 3] In all other

circumstances, confusability functions as an objective. The designer's goal is to minimize confusability so as to avoid trademark infringement, dilution and medication errors.[44, 48, 49]

Memorability. A good drug name should be memorable. It should be easily recalled and recognized.

Meaning. Drug names are the centerpiece of drug marketing and advertising campaigns. As such, they must have denotative and connotative meanings that are consistent with the marketing message. This objective can be tricky to optimize, because designers are constrained not to incorporate exaggerated or otherwise misleading claims and because the same name may mean different things to different people.

Pronounceability. Drug names must be easily pronounced and, ideally, the spelling should not invite multiple pronunciations. This objective is important for safety reasons (avoiding confusion) and for marketing reasons. People are less likely to use a product whose name they have difficulty pronouncing.

Ease of Spelling. The pronunciation of the name should not invite multiple spellings, and the name should be easy to spell.

Global registerability. The pharmaceutical industry is a global industry. Whenever possible, companies prefer to have global trademarks so that their product is known by the same name in all international markets (e.g., *Coca-Cola*®). This simplifies labeling, packaging, advertising and marketing of the product.

Competitiveness. This is one aspect of the meaning of the name. A trademark is a valuable piece of intellectual property and the central component in a marketing campaign around a drug. Thus, a good trademark must have qualities that allow it to compete effectively with existing trademarks in the same therapeutic category. It is not clear precisely what

characteristics of a name allow it to compete well with another name. At times, it appears that new names are intentionally designed to be similar to existing names, especially if the existing name is a market leader that has engendered strong good will. (Industry trademark attorneys will, of course, deny that this is done intentionally.[50]) After all, the makers of the newer drug would like the consumer to know that the new drug is a competitor of the old drug. If the name can create this impression, without infringing or diluting the existing trademark, that is desirable.

Aesthetic appeal. Aesthetic appeal is difficult to define. Generally, it refers to an overall impression of the drug's stylistic qualities. It is a complex function of a name's pronounceability, spelling, and meaning.

Length and simplicity. Based on conversations with trademark designers and attorneys, and on an analysis of existing brand and generic names, it is clear that, in brand names especially, shorter and simpler are better. This may be because short and simple names are easier to spell, pronounce, and remember, but there may be other reasons as well. However, brevity and simplicity conflict with confusability, because, all other things being equal, shorter words will have a higher number of similar neighbors than longer words.[51]

Other objectives. Although we have tried to highlight the most important and commonly pursued objectives, the preceding list is by no means exhaustive. Brand naming companies often pursue additional objectives that relate to the aesthetics and business purposes of brand names. For example, Lexicon Branding, who coined names such as *Pentium*®, *Centrino*® and *PowerBook*®, focuses on *intrinsic values* and *expansiveness* as objectives. According to their web site, "Intrinsic values are those images or ideas conveyed by a name that transcend product context. Expansiveness represents the ability of a name to support multiple messages and to grow and adapt with product change."[52] These might well fit into our "meaning" objective, but

the point is to acknowledge that there are many subtle objectives that designers may pursue within the broad outlines we have described.

Evaluating Drug Names with Respect to Key Safety Constraints and Objectives

Once a designer knows the constraints and objectives, the task is to generate designs that meet the constraints and optimize the objectives. This is done through a cycle of generating and testing various designs. The process of generating the alternative designs is an important topic in its own right, but it is beyond the scope of this paper. Instead, this section describes how one might (and how some people actually do) go about testing drug names with respect to safety objectives. By safety objectives, we refer primarily to confusability. Our broad notion of confusability subsumes memorability, pronounceability and spelling as defined above, because names can be confused in recall and recognition memory, because pronunciation problems can lead to auditory perception errors, and because spelling is related to visual perception errors. The sections below discuss expert judgment, computer methods for determining similarity, behavioral tests, and finally observational methods for determining error rates. These correspond to the main types of evaluation techniques considered by the FDA at its recent public meetings on name confusion.[1, 3]

Expert Judgment

Until recently, expert judgment was the dominant approach to pre-approval screening of drug names. It continues to be used by trademark attorneys, the U. S. Food and Drug Administration, and by the Med-E.R.R.S. subsidiary of the Institute for Safe Medication Practices.[1, 3, 15, 53] It involves showing one or more proposed drug names or drug products (i.e., names with strength, dosage form, route of administration, packaging, etc.) to a panel of experts who pass judgment on the confusability of the name or product. The opinions of multiple experts

are either compiled into a consensus report or votes from different experts are tallied. Decisions about whether to proceed with a name are then based on these expert judgments. The advantage of expert judgment is that it taps into the experience and implicit knowledge of human experts. The knowledge of human experts is notoriously difficult to articulate, formalize or simulate. Another advantage is the inherent credibility that attaches to decisions made by legitimate experts.

The disadvantage of expert panels is that they may not know or be able to recall all of the possible products that might be confused with a proposed name. In addition, expert opinions may vary within the same individual over time and across individuals. Group-think can undermine independent decision making on expert panels, and consensus building processes may mask extreme views or differences of opinion.[54, 55] In spite of these difficulties, because of the importance of credibility and accountability, final decisions about drug names (in fact all drug approval decisions) at the FDA are made by panels of human experts. Thus, all of the other methods for evaluating drug names with respect to design objectives should be seen as providing input into the eventual process of human expert judgment.

Computerized Searching Using Objective Measures of Similarity

One method for identifying potentially confusable names is to search a database of existing names using the new name as a query. This type of trademark searching has a long history, and these services are widely available on the web. A Google search on the phrase "trademark search" yields 51,700 hits. Each trademark search returns a number of existing names that are more or less similar to the query name. Although search methods differ widely between companies, the basic idea is the same. Similarity is presumed to be highly correlated

with confusability, so similar names are identified as potentially confusable. Fundamentally, this is a sound approach, and one we have been encouraging regulators to use for years.[56]

If we imagine that all drug names exist in a multidimensional space whose dimensions correspond to orthographic (i.e., spelling) and phonemic (i.e., sound) features, Figure 1 would graphically illustrate the current and ideal situation in drug naming. In the current situation, names are distributed in a somewhat random or haphazard manner throughout the name space. Panel (a) of Figure 1 was created by generating 100 random (x, y) pairs. In reality, names are not placed in this space randomly. A significant effort is made to minimize the likelihood of confusion. In fact, most names are not very similar to other drug names.[24] Nevertheless, because this effort has not been fully quantified and systematized, there are regions of the name space where two or more names cluster together in dense neighborhoods. An example of a name from a dense orthographic (i.e., spelling) neighborhood is *Dynabac*®, whose neighbors included *Synalar*®, *Rynatan*®, *Dynapen*®, *Dynacirc*®, and *Dynacin*®. Another name from a high density orthographic neighborhood is *Virilon*®, whose neighbors included: *Verelan*®, *Uridon*®, *Trilion*®, *Miradon*®, and *Daricon*®.[57] These dense neighborhoods of the name space tend to be hot spots for confusion.[57] An example of a name from a sparse neighborhood is *Flexeril*®, which had no neighbors in the database we examined.[57] Panel (b) illustrates the ideal name space, one in which each name is separated from each other name by some minimum "zone of safety." Note that these are not graphs of any actual names. They are merely used to illustrate the underlying point. By approaching the confusability objective quantitatively and systematically, the goal is to make the name space look more like panel (b) than panel (a).

Insert Figure 1 about here.

The FDA's announcement, at the December 4, 2003 meeting of the Drug Safety and Risk Management Advisory Panel, that they would begin to use a computerized search system is a step in the right direction.[3] There are, however problems and challenges associated with this approach.

Lack of evaluative data on similarity measures and retrieval methods. The most important point about the quantitative approach to similarity and confusability is that not all similarity measures are created equal. This fact has been well established in the literature on information retrieval[58, 59], but has not had sufficient impact on the practice of trademark searching. Many well-known trademark searching services do not even return *ranked* lists. Those that do rank retrieved names by similarity rarely describe the underlying similarity measures, and none of the commercial search services have subjected their retrieval methods to an objective evaluation. As drug name searching has increasingly become a topic for academic research, more systematic evaluations have begun to appear.[60, 61] If the results of computerized searches are going to be used to make regulatory decisions, the underlying search methods must be validated.[62] There are no peer-reviewed publications validating the software recently adopted by the FDA, although at least one such validation study has been submitted for publication.[63]

One approach to validation has been to use published lists of previously-reported drug name confusion errors as a gold standard, and then to develop methods that can discriminate between name-pairs on this list and name-pairs not on this list.[56, 61, 64] Unfortunately, these published lists are compilations of *voluntary* error reports. They *must not* be viewed as a gold

standard. Some names appearing on the lists are near misses not actual errors. They thus have questionable status as true positives. Due to underreporting, pairs of names not appearing on such lists may in fact have been involved in errors but not reported. In this context, absence of evidence cannot be interpreted as evidence of absence, i.e., as a true negative. Since any test method will be validated by assessing its ability to distinguish between truly confusing and truly non-confusing names, the ambiguity around true positives and true negatives in databases of voluntary reports is highly problematic. A related quandary concerns the need for the proportion of true positives and true negatives in the test sample to be the same as the real-world proportion of true positives and negatives, but we do not know these real-world proportions. Without these real-world population values, it is not possible to determine the positive or negative predictive value of a screening test.[65, 66]

The best approaches to validation of information retrieval systems involve the method of pooled relevance judgments, used by the National Institute for Standards in their large scale evaluations of text retrieval systems.[67] An alternative involves comparison between computer predictions and behavioral tests of confusion. A recent evaluation study illustrated how a ranked list of retrieved names can be compared to expert judgments of relevance or similarity.[58, 60] Related work on visual perception and short-term memory illustrates how objective similarity measures can be validated against behavioral tests of confusion.[16, 18, 57]

Before moving on, it should be noted that comparative evaluations are not the only things lacking. Also lacking are good methods for comparing similarity measures to some reference standard. Researchers have published descriptive statistics for similarity for a large population of brand and generic drug names[24], but more still needs to be done to help people understand, in absolute terms, what each level of similarity means and how similar is “too similar.”

Name similarity is not enough. The majority of commercially available trademark searching services focus on names only, in spite of the widespread recognition than similarity in non-name attributes such as strength, dosage form, route of administration and administration schedule increases the probability of error.[60, 68] Much more research is needed to determine how to quantify similarity in non-name attributes and to discover how similarity in these other attributes interacts with name similarity to affect the probability of confusion.

Name similarity is itself multidimensional. The similarity between two names depends on the mode of communication being used. The main modes are writing (look-alike) and speech (sound-alike).[61, 64, 69] But look-alike similarity depends on whether the name is handwritten or typewritten. In one well-publicized case, *Coumadin*® and *Avandia*® were confused due to poor handwriting.[70] Computerized methods for detecting similarity between handwritten names have been proposed, but not thoroughly tested or widely adopted.[71] Objective measures of different dimensions of similarity (e.g., typewritten, handwritten, spoken) will produce different rankings and predictions about confusability, and little work has been done to determine how these divergent rankings should be merged or integrated into the decision-making process.

Similarity does not always increase confusability. The basic assumption underlying quantitative approach to similarity is that similarity increases confusability and, therefore, all other things being equal, that similarity between names should be reduced. This assumption is often valid, as in the case of visual perception[57], auditory perception[72], and recognition memory.[16] However, in the case of free recall of lists of drug names, greater similarity actually leads to better recall (because rhyming can be used as a cue to facilitate recall).[18]

Similarity is not symmetric. Another problem with present-day similarity searches is that the measures of similarity (e.g., edit distance[56, 61], ngram similarity[56, 61], phonetic

alignment distance[63, 69, 73, 74]) are symmetric. In other words, current similarity measures assume that *Sim*(A,B)=*Sim*(B,A). In a well known and widely-cited paper, Tversky has shown that many human similarity judgments are *not* symmetric, i.e., *Sim*(A,B)≠*Sim*(B,A).[75] The same has been shown specifically for judgments about linguistic stimuli.[76-78] One of the main causes of the asymmetry in similarity judgments is that names are not equally salient or prominent in people's minds. It turns out that salience/prominence exerts a powerful effect on judgments of similarity, such that a more prominent name will be judged much less similar to a less prominent name than vice versa (e.g., *Premarin*® should be judged less similar to *Primaxin*® than *Primaxin*® is to *Premarin*®).[79] This fact has important implications for asymmetry in the probability of confusion.

Probability of confusion is not symmetric. Almost all currently used methods for measuring similarity assume that if drug name A and drug name B have a certain similarity, then the probability that A will be substituted for B is equal to the probability that B will be substituted for A. This assumption is rarely explicit. Rather, it is implicit in the way names are ranked in retrieval systems and in the way people reason about similarity and confusion. In fact, the probability of confusion (A to B vs. B to A) is often not symmetric[75], because there is more to confusability than similarity. The crucial missing variable is (prescribing) *frequency* (which is itself a proxy measure of familiarity, prominence, salience, etc.). Frequency is perhaps the single most important variable in psycholinguistics, and it has powerful effects on word memory and perception.[57, 80-88] Generally speaking, common words are easier to recall and identify than rare words. Imagine that Drug A is common and Drug B is rare and that A and B have similar names. When Drug A is prescribed, it is extremely unlikely for it to be mistaken for Drug B. But when Drug B is prescribed, there is a much higher probability that Drug A will be dispensed instead,

because the pharmacist is biased by previous experience to expect the more common name.[79] The important lesson from all of this is that estimates of drug name confusability must be based on frequency-weighted similarity, not similarity alone.[57, 72, 89] It also means that pre-approval evaluation of drug names must involve some estimate of the new name's frequency as well as its similarity to existing names.

Likelihood of confusion does not capture likelihood of harm. The overriding concern is to prevent the harm that may result when a patient gets the wrong drug. But a focus on the likelihood of confusion do not capture the extent of harm that may result from a name confusion. Harm is the product of the probability of the error, the number of opportunities for error, the amount of harm caused by each error, and the probability of failing to catch the error.[57] It is possible to estimate each of these quantities. The probability of error can be estimated based on the frequency-weighted neighborhood characteristics of a name or by direct observation of lab experiments or high-fidelity simulations. The number of opportunities for error is the number of prescriptions written or dispensed for a given drug name over a given period of time. The amount of harm caused by each error is the most difficult to predict, since it depends on the toxicity of the dispensed drug, the physiological need for the intended drug, the duration of exposure to the wrong drug (or lack of access to the right drug), as well as the resilience of the patient. The best approach here is to focus on high alert drugs (e.g., concentrated electrolytes, opiate analgesics, chemotherapy drugs, paralytic agents, anticoagulants, insulin). Finally, the probability that an error will fail to be noticed might be estimated from past experience or based on the visibility of the physiological consequences.

The pair may be the wrong unit of analysis. Most of the work on pre-approval screening has focused on the name *pair* as the crucial unit of analysis and decision making,[56, 63,

[64] with similarity between pairs seen as the main causal factor. There are two reasons to question whether the pair is the appropriate unit of analysis. First, regulators must approve *individual names*, not *pairs*, so evaluative metrics should also be based on individual names, not pairs. Any proposed name will likely be similar to several existing names. Pre-approval metrics should yield summary measures of confusability that take into account the frequency- and severity-weighted similarity between the proposed name and all of the existing names in its "neighborhood."[89-91]

Second, any method that takes the pair as the unit of analysis is likely to perform poorly on scientific measures of predictive usefulness. One such measure, positive predictive value, refers to the probability that a prediction will be correct when a test yields a positive result.[61] Clinical epidemiology texts provide the relevant mathematical details.[65, 66] Positive predictive value decreases as the frequency of the event in question decreases. The rarer an event, the more likely that a positive prediction will turn out to be a *false* positive.

If the pair is taken as the unit of analysis, then the relevant population is all possible pairs. For N names, there are $(N^2-N)/2$ possible pairs. As N increases, the number of possible pairs grows quadratically. Thus, if there are 4,300 one-word drug names in use in the U.S., as Table 1 might suggest, then there would be 9,242,850 possible pairs of names. If one expands to include all names, not just one-word names, then there are perhaps 60 million pairs. Our largest list of reported error pairs contains about 1250 pairs, suggesting that *reported error pairs* represent 1250/9.2 million = 0.01% or, even worse, 1250/60 million = 0.002% of the possible pairs.[50] At these levels of prevalence, predictive models must have extremely low false positive rates in order to be useful. Even if one could develop extremely specific tests of pair-based confusability, sensitivity trades off against specificity. Very specific tests are likely to miss most genuinely confusing pairs (i.e., the false positive rate will be low, but the false negative rate will

be high). Even if the number of reported pairs is a dramatic underestimate due to under-reporting of actual errors,[92] performance is still likely to be poor when predictive models use the pair as the unit of analysis.

One solution is to use the individual name as the unit of analysis, thereby avoiding the explosion in population size that results from focusing on pairs. If one assumes there are 1000 unique names in the published list of name confusions, and perhaps 11,000 names in use, then the prevalence of confusing names increases from 0.01% in the pair-based analysis to 9% in the analysis based on individual names. At this level of prevalence, predictive models stand a better chance of being useful. Still, since estimates of harm require information about *which* names are confused, not just *that* a name will be confused, some attention will still have to be paid to pairs.

Evaluating Short-Term Memory

There is a vast literature in psycholinguistics that provides detailed descriptions of experimental techniques for assessing the memorability of words.[93] Basically the techniques involve showing participants a set of words to be remembered (the study list) and then asking them either to recall the words from memory or recognize the study list words from among a lost of distractors.[16, 18]

Evaluating Perceptual Accuracy

Methods for assessing accuracy in visual and auditory perception are quite similar, except for obvious differences between visual and auditory stimuli.[57, 72] There are several related tasks that get studied under the general heading of "word recognition." These include lexical decision (i.e., is the stimulus a word or a nonsense string), naming (i.e., how long does it take to pronounce the stimulus word), same-different discrimination (i.e., when presented with two stimuli, determine whether they are the same or different) and perceptual identification (i.e.,

when briefly presented with a stimulus, correctly identify it). Interested readers should consult a general reference on psycholinguistics.[94]

Observational Methods for Determining Confusability

In addition to laboratory-based, traditional psycholinguistic experiments, other methods for determining confusability have been proposed. Barker and his colleagues have pioneered a method for direct observation of medication dispensing and administration.[7, 10, 95, 96] The method uses trained individuals to directly observe pharmacists, nurses and physicians as they order, dispense, and administer drugs. This method can be expensive and time consuming, especially due to the low base rate of errors, but it does not suffer from many of the validity and generalizability problems that other methods face. Regrettably, it is not clear how to use this method for *pre-approval* screening. Since, by definition, proposed names are not yet being used in real patient-care settings, the method of direct observation may be of limited value for pre-approval screening.

An analogous method which may work in the pre-approval setting involves direct observation of high-fidelity simulations.[97] The setting being simulated may be a retail pharmacy, a hospital pharmacy, or, in theory, any other patient care setting. The method involves placing health professionals in the simulated setting and observing them as they order, dispense, or administer drugs. One advantage of this approach is that the experimenter can control various aspects of the setting, such as the noise, lighting, presence of distractions, number of prescriptions filled per hour, and so on. The key challenge is to make the simulation as realistic as possible in order to avoid external generalizability problems. Another disadvantage is cost. Truly high-fidelity simulated pharmacies can be prohibitively expensive to construct and maintain.

Still other strategies have been proposed. NDC-Health, an information services provider to health care companies and pharmacies, proposed at the June 2003 FDA meeting on name confusion[1] that electronic orders for simulated prescriptions could be sent through their existing claims-processing network. These prescriptions would use proposed new names. The test would be to see whether the pharmacist filled the prescription with another, similar existing drug or whether they rejected the prescription because it called for a non-existent product. This proposal has the advantage of collecting data from real-world settings, but it fails to address the fact that pharmacists would be relatively unfamiliar with the proposed name being tested. This would compromise the validity of the test in some respects. But the proposal may strike a balance between high fidelity simulations and direct observation. This technique has yet to be tested.

Summary of Evaluative Techniques

No single method will adequately address the needs of pre-approval screeners, just as no single assay or experimental design can address all of the pre-approval questions about a drug's safety or efficacy. What is needed is a battery of tests that, taken together, evaluate proposed names with respect to each crucial safety objective. Just as there are Phase I, II, and III clinical trials to determine pre-approval safety and efficacy, as well as Phase IV trials to determine post-marketing safety and efficacy, a multi-stage, multi-method approach is needed to establish the safety of drug names. The challenge is to identify, develop, and, most importantly, to validate such a battery of tests for confusability.[62]

Selecting a Name from Among Equally "Optimal" Candidates

Once one has generated a list of candidate names, checked that the names meet all relevant constraints, and evaluated the names with respect to multiple objectives, what remains is to select *the* name that will be used for a given drug. This choice might seem obvious—just pick

the name that scores highest on all of the objectives. If it were the case that a single name scored highest on all relevant objectives, the choice would be easy, but this rarely happens. Instead, because objectives trade off against one another, names which score well on one objective tend to have lower scores on other objectives. The most common scenario is that no single design (i.e., name) outscores the other designs on all objectives. One is typically left with a set of names that are, in a sense, equally optimal. If, for a given design, no objective score can be increased without decreasing another objective score, then the design is said to be *Pareto optimal* (or non-dominated or efficient).[98] The goal of modern multiple objective decision making is to identify the Pareto-optimal set of designs.[33, 34] Several related techniques for selecting a final design from that set are available: (a) weighted sum optimization, (b) deviation sum minimization, (c) constraint oriented strategy, (d) multilevel programming (preemptive optimization), and (e) the minimax formulation strategy.[33, 35, 99-103] Although each method is distinct, they share several common features.

Weighted sum optimization involves assigning a weight to each individual objective and then optimizing the weighted sum. The advantage of this approach is that it effectively transforms the multiple objective problem into a much more easily solved single objective problem. The disadvantage is that the user must specify the weights for each objective, and it is difficult to do so with confidence and precision. Different weights may lead to very different "optimal" designs, so the selection of weights is crucial.[99, 101, 102]

Deviation sum minimization involves setting a goal value for each objective and then minimizing the weighted sum of the differences between each objective and its target value. For example, the designer might specify that the goal for name length is 3 syllables and eight characters. Each candidate design can then be evaluated with respect to the target values on each

objective, and the design whose weighted deviation from the multiple target values is the smallest is selected. Related to the deviation sum approach is the minimax formulation approach. The minimax formulation strategy begins by computing the optimal value of each separate objective. Then the design is selected that minimizes the maximum relative deviation of any objective from its optimum.[99, 101, 102]

Another alternative is to use a constraint oriented strategy.[99, 103] In this approach, the user defines a "good enough" value for all but the most highly ranked objective. The designer then identifies the designs that optimize the highest priority objective, subject to the constraint that the scores on all less important objectives are good enough. Applying this strategy to a large subset of candidate designs will reduce it to a much smaller subset, each of which is optimal with respect to the highest priority objective while still being good enough with respect to all of the other objectives. Selection from among equally good alternatives can be done arbitrarily, based on subjective preference, or based on application of one or more quantitative objectives to the set of good enough designs.

Closely related to the constraint-oriented strategy is preemptive optimization.[99, 101, 102] In preemptive optimization, the designer begins by ranking the objectives in priority order. Then one selects the designs that optimize the highest priority objective. Achievement of the optimal value on the highest priority objective is then set as a constraint, and attention is focused on the next highest priority objective. The designer searches for the designs that optimize the second most highly ranked objective, subject to the constraint that they do not diminish the optimal score on the first ranked objective. For example, the designer might choose memorability as the most important objective and select the names that score highest on memorability. If length were the second most highly ranked objective, then the shortest names among the most memorable

names would be selected. This process would continue until all of the objectives were examined in rank order. If multiple designs exist after all objectives have been sequentially optimized, then selection of the final design must me made somewhat arbitrarily.

Discussion and Conclusions

The incidence of drug name and drug product confusions made by patients and practitioners alike demands that manufacturers and regulators continue to improve their ability to design and approve safe drug names. This essay provides a framework for thinking systematically about drug name design as a process of multiple objective optimization. Concerned parties must work together to identify the key objectives, to determine how names will be evaluated with respect to these objectives, and to determine how these evaluation methods can be validated. Recent steps taken by regulators, as well as ongoing efforts by the manufacturers and name screening companies, appear to be heading in the right direction, but many pitfalls lie ahead.

Perhaps the most vexing problem concerns confusions between drug products that are already on the market. Regulators have been extremely reluctant to force name changes. So strategies are needed for minimizing confusion between existing names. In the absence of name changes, system and process improvements are needed. We know of no better approaches than those that have been recommended frequently before[19]: (a) prohibit or restrict handwritten and spoken medication orders; (b) exploit the power of bar codes, computerized physician order entry, and computerized decision support; (c) develop non-alphabetic storage of drug products; (d) separate previously confused products; (e) use tall man lettering to highlight distinctive parts of confusing names; (f) eliminate one half of a confusing pair from the formulary if an equivalent, non-confusing alternative is available; (g) improve human factors (e.g., lighting,

noise, workflow, fatigue) in dispensing areas; (h) include the reason for use on the prescription; (i) use both brand an generic names when either one alone may cause confusion; (i) minimize or eliminate abbreviations. Many of these strategies are of proven value but have not been widely implemented.[22, 104-107]

Our discussion has assumed a perfectly rational designer who is willing to rank safety objectives above other commercial objectives. These assumptions may not be valid in a world where billions of dollars in sales are perceived to be linked to the choice of a trademark, where industry trade associations question the role of trademarks in wrong drug errors, and where errors are often seen as inevitable and unpreventable. In addition, many of the evaluative measures that will be needed have either not been developed or not been adequately validated. In addition, there are conflicts of interest to be concerned about, especially if the people doing the safety screening for a name also have a financial stake in the name's eventual acceptance.

These closing comments are meant to illustrate that the challenge of designing safe drug names is not only a technical challenge. No doubt, there are daunting technical problems to be solved, but even if we had perfect measures of confusability, it would still not be clear where the line should be drawn between acceptably confusing and unacceptably confusing names. Nor has it been convincingly shown whether or not the time and money being spent on pre-approval screening of names might be better spent on system improvements such as bar coding or computerized physician order entry. These and many other issues must be confronted as we continue our efforts to design safe drug names.

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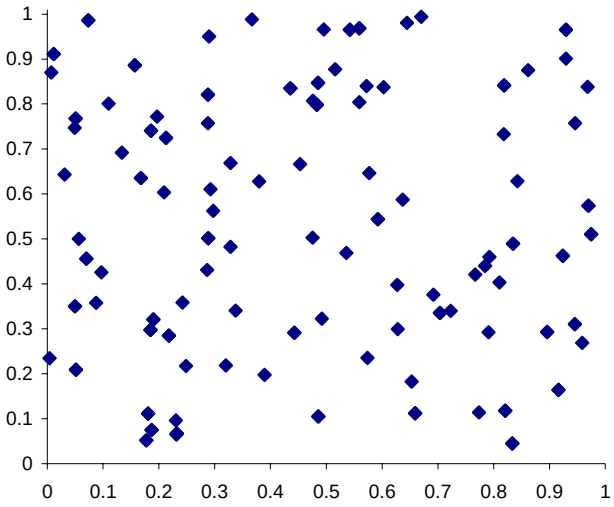
(a)



(b)

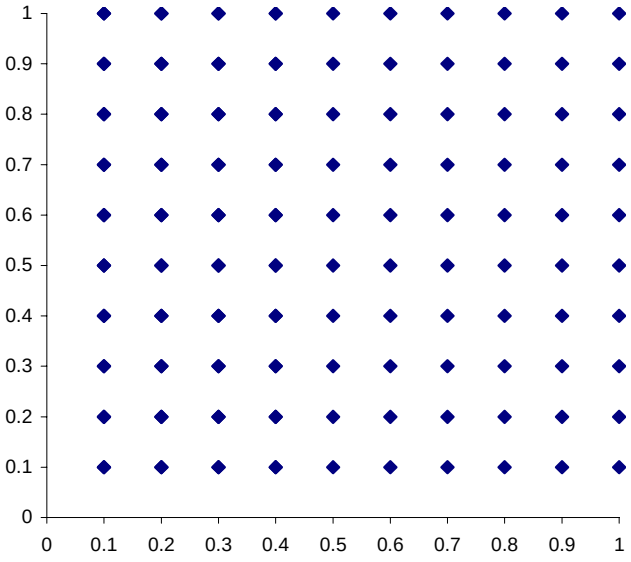


Figure 1. Each point represents the location of a name in a multidimensional space of names. Panel (a) depicts the current name space, with names randomly distributed within the space. Most names are not close to one another, but pairs and clusters of very similar names do exist. Panel (b) depicts the ideal name space, in which each name is surrounded by a minimal "zone of safety."