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Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane
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RE: Docket No. 2003N-0201 - Request for Comments: Minimizing Medication Errors -- Methods for Evaluating Proprietary Names for Their Confusion Potential

Merck & Co., Inc. is a leading worldwide human health products company. Merck Research Laboratories (MRL), Merck's research division, is one of the leading U.S. biomedical research organizations. The medicines which Merck ultimately presents to worldwide health authorities for marketing approval are those that have met the highest standards available and those that are able to withstand the most critical regulatory review.

Merck supports regulatory oversight of product development that is based on sound scientific principles and good medical judgment. Regulators must be reasonable, unbiased and efficient when they review the quality, effectiveness and safety of our products. Merck has participated with health authorities from around the globe in the harmonization of regulatory standards under the auspices of the International Conference on Harmonization (ICH), the objectives of which have been to identify and correct unnecessary redundancies and time-consuming inefficiencies in development of pharmaceutical products caused by incompatible regulatory schemes. We continue to monitor the equitable and consistent application of these harmonized standards to product development in order to ensure that *new* or *improved* therapies reach patients as swiftly as possible.

In the course of bringing product candidates through the approval process Merck is routinely confronted with identifying and selecting unique trademarks for new products. Because of our vast experience in trademark evaluation and selection and our familiarity with the current methods for trademark evaluation we are very interested and well qualified to respond to FDA's request for comments on the issue of evaluating proprietary names for pharmaceutical products.

Background

In the May 30, 2003 Federal Register (68 FR 32529) FDA published notice of a public meeting and request for comments on methods for evaluating proprietary names for confusion potential to minimize medication errors. Written comments or answers to questions posted on the web site of the Center for Drug Evaluation and Research (CDER) were requested by July 15, 2003.

Subsequently, FDA re-opened the comment period by notice in the August 6, 2003 Federal Register (68 FR 46646) to allow the public until September 5, 2003 to respond.

The questions on which FDA sought comment were posted on the CDER web site prior to the June 26, 2003 workshop. (See http://www.fda.gov/cder/workshop.htm.) FDA's questions are repeated below along with our responses.

1. *Are methods currently employed by sponsors and FDA appropriate for evaluating look-alike and sound-alike names? Examples of methods currently being used include handwriting and voice recognition studies, computer tools, expert committee analyses, and questionnaires/surveys.*

The question should not be whether currently employed methods are appropriate for evaluating look-alike and sound-alike names. Instead, we should ask whether current methods are capable of *evaluating the risk* of medication errors if a proposed trademark is put into use. The current methods referred to in the question have not been validated for their ability to evaluate the risk of medication errors or to yield reproducible results.

This question is based on the belief that look-alike and sound-alike names are a significant cause of medication errors. We believe that prior to determining methods and approaches for evaluation, the role of look-alike and sound-alike similarity as being a contributing factor of medication errors needs to be investigated and understood. It is not possible to use statistics from the available data that we have seen published to determine to what extent medication errors are attributable to name/name similarity. Once one goes beyond an identical, or near identical, name, the role of look-alike and sound-alike similarity as a contributing factor in medication errors becomes increasingly uncertain.

Medication errors are multifactorial in origin. Factors that have been identified as causes of error include performance deficit; failure to follow procedure; transcription errors; errors in documentation; computer entry errors; communication errors; knowledge deficit; distribution system failures; written and oral orders that are confusing, incomplete, or misunderstood; and illegible or unclear handwriting. Additional contributing factors include distractions, inexperienced staff, insufficient staff, and

increased workload.[1] The use of sound-alike and look-alike names, both established names and trademarks, has also been identified as a contributing factor to medication errors. However, it is axiomatic that every medication error involving two products will use two drug names as a means to identify the error. This does not mean that name/name similarity is the cause of the error.

Clearly, consideration should be given to putting in place effective interventions that mitigate the factors which contribute to medication errors. The fact that industry, FDA, and a growing number of private organizations are paying serious attention to the selection, approval, and post-marketing monitoring of trademarks for pharmaceuticals is, in itself, an intervention that should reduce any contribution of drug name similarity to these errors. Current methods of evaluation focus attention on careful selection of a trademark to avoid similarities with other marks in the market place. These methods are based on the *presumption* that the risk of medication errors involving the substitution of one product for another increases as the degree of similarity between trademarks increases.

All current methods devolve to subjective judgments or informed opinions by "experts" about the risk posed by the trademark. Methods in current use, however, are not designed to evaluate the risk of a substitution error or the relative risk posed by varying degrees of similarity. This is abundantly evident from the fact that FDA's Division of Medication Errors and Technical Support (DMETS) reports that, on average, they reject 1/3 of the trademarks submitted to them in spite of extensive industry efforts to eliminate similarity with other marks and names. A number of different methods are currently employed by various companies and contractors to evaluate trademarks. Methods include expert committees of various sizes, and written and oral prescription simulation studies using varying numbers of subjects and varying numbers of handwriting and voice samples. While current methods may increase our comfort with our final judgments, none provide objective evaluation of risk and, therefore, we are left with only the presumption that the effort has minimized potential risk. As is clear from the June 26 Public Meeting, there is no current "testing" method that produces reliable, reproducible and validated results.

Current methods develop information that is intended to help to inform subjective judgment. The subjective decision should be based upon a reasonable evaluation and interpretation of this information. The final determination, however, needs to recognize the limitations of the information in producing a valid outcome, and the benefits of the trademark as well as risks. It must recognize that there are clear safety benefits to trademarks which, unlike established names developed through the USAN process, do not share common stems within classes, are generally shorter (and therefore, less subject to mispronunciation, misspelling, and the temptation to abbreviate), and are more easily

[1] "Summary of Information Submitted to MedMARX in the year 2000," United States Pharmacopeia

remembered by health care professionals and patients. A particular mark may offer safety benefits because it is a global trademark, an increasingly important factor with the spread of Internet use as a source of information.

There is a clear need for further development of methods, including computer tools and linguistic principles, that will produce reliable, reproducible, and validated results. The June 26 workshop was an excellent start in the process.

2. *In studies designed to evaluate potential prescription errors: (a) What is an appropriate study design? (b) What is the appropriate size for an expert committee or for a prescription drug (written and voice recognition) study? (c) What should be the composition of a group of evaluators (e.g., what proportion of physicians, pharmacists, nurses, consumers)? (d) What are appropriate outcome measures?*

The term "studies" in the context of the methods currently being employed to evaluate trademarks is a misnomer that contributes to misunderstanding what we are doing now to improve the adoption of names with a minimal risk of confusion. "Studies" implies there is a hypothesis being tested and a standard against which the results are evaluated. In general, none of these conditions apply to the evaluative methods currently in use. Before getting to questions related to the appropriate size and make-up of panels or "test subjects", the question that needs to be answered is whether we can design actual studies to assess the risk. A decision could then be made regarding the acceptability of that risk. To do that, you need a validated model. The focus should not be on testing for name similarity but on ways to test the risk that name similarity may contribute to medication errors. We need to answer such questions as how to frame the hypothesis for such studies, whether reasonable standards can be developed against which results can be evaluated, what constitutes high risk name similarity, and whether name similarity is a good surrogate for error potential.

3. *What kind of information (e.g., drug name, strength, quantity, directions) should be included in verbal or handwritten prescription drug studies?*

The short answer to this question is that until a validated, reproducible model is identified, the details of the studies cannot be defined. In exploring ways to evaluate the risk of name similarity, however, it should be recognized that the information included in the studies will depend on the study objectives. If, for example, the test is intended to generate the greatest possible number of names with some similarity, restricting the study participants' ability to "interpret" the order based on ancillary information would suggest that only the product name need be provided. In such a "test," evaluation of the results by the safety evaluator should include consideration of, and greater weight assigned to,

mitigating factors such as differences in strength, directions for use, patient population, and patient age and gender between the proposed trademark and the names identified as "similar." Mere similarity in names by itself does not establish greater risk of medication error. Prescription analysis testing that includes cues that are normally part of a pharmacist's interpretation of a written or verbal order (such as strength, directions for use, and other cues) may call for the safety evaluator to rely less upon this information as factors mitigating the risk of misidentification when it occurs in the test environment. However, as was pointed out in the June workshop, current testing lacks most of the basic tenets of basic research design and, therefore, results, either positive or negative, are of no predictive value.

Where testing includes additional information beyond the proposed name of the product, the amount of information provided should be adequate to represent a "fillable" prescription were it received in a pharmacy. If, for example, the new product will be marketed in more than one strength, the strength of the product should be included. Because prescriptions continue to be written with instructions such as "as directed," it is acceptable for outpatient written prescriptions to be presented in name evaluation programs bearing these "directions for use," although it would be preferable to provide specific directions for use. Outpatient orders should also include a quantity to dispense if the instructions for use are "as directed" or if the product is intended for "prn" use. Inpatient written orders should always include instructions for use because drugs in such settings are not self-administered. Quantity need not be specified. As a general rule, physicians don't specify dosage form except where there are multiple dosage forms and a specific form is required (a liquid for pediatric patients, for example). For the most part, physicians specify route of administration in inpatient orders; for outpatients, the oral route is presumed unless another route or a specific dosage form is ordered. Therefore, dosage form need not be included in sampling tests.

4. *Sometimes similar drug names are approved contingent on a pre-marketing agreement for a risk management program. Describe examples of effective risk management programs (e.g., an educational campaign) that could be used to minimize look-alike, sound-alike confusion. How should the effectiveness of a risk management program be evaluated?*

The temptation to implement a solution before defining the problem is manifest in this question. We recommend against such an approach. Instead, all stakeholders should be brought together, first to understand the problem and its multi-faceted causes; second, to devise potential solutions; and, finally, to evaluate their effectiveness.

A pre-marketing agreement for a risk management program can be an effective means of minimizing the potential for error in those occasional cases where such potential is

reasonably established, but can be lessened to a level that avoids such likelihood by taking certain intervening actions. We do not believe a risk management program should become routine for all trademarks, but in certain limited cases where the risk of error can be reasonably established and an intervention will likely reduce such risk to a level that reasonably avoids the risk, a specific, limited, risk management program does appear appropriate.

Unless one has some way to evaluate the effect of a trademark on the risk of a medication error (other than subjective opinion), it is impossible to design a risk management program to reduce that risk. Similarly, it is impossible to evaluate the success of such a program. Currently, to our knowledge, no one has any idea what magnitude of reported name confusion constitutes an excess over the rate from random error alone in the prescribing and distribution of pharmaceuticals. Further, the relationship between the rate of reporting and the number of actual errors is open to speculation. The contribution of putative name similarity in promoting dispensing errors is unknown, as is the number of errors prevented by a unique trademark that replaces a multisyllabic generic name with similarities to other products in the same class. It has been argued that replacing handwritten and verbal orders with electronic ordering and implementing bar-coding to double check the dispensing function (two risk-management strategies) will reduce medication errors. A recent review of the literature on these technologies found that insufficient research has been done to confirm their value.[2] In sum, we can't differentiate random error rates from system error rates and we cannot quantify the contribution of the various factors that contribute to medication errors. Therefore, any risk management system imposed upon approval is of unknown value because it is based on speculation about the risk of error, supposition about the role of the trademark with regard to the assumed risk, and presumption that the prescribed intervention will have a positive outcome.

5. *Should there be different trade-name evaluation procedures for different classes of drugs (prescription vs. over-the-counter)?*

We believe that different methods are needed to evaluate the risk of product confusion in the OTC arena for a number of reasons. Consumer self-selection is the primary factor guiding the purchase of OTC products and, therefore, the "audience" for OTC labeling is different than that for prescription drug products. While the same kinds of errors may occur with OTC products as occur with prescription drugs when OTCs are ordered in a hospital or custodial care facility, mistakes in self-selection of OTC products may occur as a result of deficits in consumer knowledge regarding the array of OTC products available and differences in general educational level. The degree to which consumers

[2] "Impact of Emerging Technologies on Medication Errors and Adverse Drug Events", American Journal of Health-System Pharmacy, 60(14) 1447-1458, American Society of Health-System Pharmacists, 2003.

rely upon trademarks in selecting products may be different than that of health professionals involved in prescribing and dispensing. In addition, the consequences of a medication error involving misselection of an OTC product are also likely to be different. Because of these differences, different procedures for assessing risk of medication errors related to trademarks for OTC products probably are warranted.

Currently, OTC products that reach the market via the OTC Monograph route undergo no prior FDA review and, therefore, trademarks for such products are not subject to evaluation by the Agency. Thus, there is the potential for such trademarks to inadvertently conflict with a mark for a prescription product or an NDA-based OTC product that has been reviewed and approved by the Agency.

We welcome the opportunity to comment on this important issue and, if appropriate, to meet with you to discuss these issues.

Sincerely,

for David W. Blois, Ph.D.
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