



Centers for
Education &
Research on
Therapeutics

a program of the Agency for Healthcare Research and Quality

July 6, 2004

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, rm. 1061
Rockville, MD 20852

Re: Draft Guidance for Industry on Development and Use of Risk Minimization Action Plans;
Docket No. 2004D-0188.

The Centers for Education & Research on Therapeutics (CERTs) appreciate the opportunity to comment on the draft Guidance prepared by the FDA related to risk minimization action plans. The CERTs demonstration program is a national initiative to conduct research and provide education that advances the optimal use of drugs, medical devices, and biological products. The program, authorized by Congress as part of the FDAMA 1997, is administered and funded as a cooperative agreement by the Agency for Healthcare Research & Quality (AHRQ), in consultation with the Food and Drug Administration (FDA). Seven centers (each with a particular population focus), a Coordinating Center, a Steering Committee, and numerous partnerships with public and private organizations make up the CERTs program. Over 200 research and education projects are included in the CERTs portfolio.

Risk management is a critical topic to advance the optimal use of therapeutics. One CERTs initiative aimed at addressing risk management was the organization of a series of “think tank” workshops to identify priority research issues that could improve the nation’s ability to assess, communicate, and manage therapeutic risk called the Risk Series. The priority research issues resulting from the Risk Series were announced in March 2003 (see http://www.certs.hhs.gov/programs/risk_series/index.html).

Our comments are shaped by the results of the CERTs Risk Management “think tank” Workshop (January 2003), as well as the CERTs experience in studying issues related to assessment and management of therapeutic risks in the context of their benefit.

The Guidance is consistent in a number of aspects with the recommendations of the CERTs Risk Management Workshop participants:

- Promotes the goal of maximizing benefit
- Recommends input from all stakeholders
- Recommends evaluation of tools prior to implementation
- Recommends posting general information on the effectiveness of tools on an FDA website
- Specifically asks sponsors to consider whether a recommended RiskMAP will preserve access to the product for patients

An important difference between this document and the recommendations of the CERTs Risk Management Workshop may derive from the use of a different definition for “Risk Management”. The definition of Risk Management in the Guidance is the combination of “Risk Assessment” and “Risk

Minimization.” We recommend that you adopt the definition of risk management used agreed upon by the CERTs Workshop participants: “an endeavor applied to the use of therapeutic products that seeks to assure that benefits to patients outweigh risks.” This definition includes evaluation of benefits, proactive monitoring for pre-clinical and post-market safety and, as needed, structured action programs.

Below are some specific comments and suggestions related to RiskMAPs.

Section III. The Role of Risk Minimization and RiskMAPs in Risk Management

The Guidance suggests that the recommendations “pertain only to situations when a product may pose an unusual type or level of risk.” In contrast, the CERTs Workshop participants recommended that “All new products should have a risk management plan.” The Workshop participants had envisioned sponsors thinking through a proactive plan for all new products to assure that benefits to patients continue to outweigh risks when the transition is made to conditions of general use. For example, a product that prior to approval was not studied in patients with co-morbid illnesses or with a wide variety of concomitant medications, could be monitored proactively after approval to assure that benefits continue to outweigh risks under conditions of general use. This approach is not fostered in the Guidance, although the Premarketing Risk Assessment Guidance does promote increasing the diversity of the premarketing population studied. We strongly recommend that the Guidance suggest that a company have a risk management plan, tailored to the unique risk/benefit profile of that drug, for every new product.

The CERTs suggest that we should attempt to define the continuum of risk for therapeutic products and come up with some general recommendations that would promote uniform application of risk management programs for products with similar levels of risk. For high risk products, those that require a strategic approach with substantively greater effort to achieve favorable risk/benefit balance, a RiskMAP should be required.

The Guidance also addresses the question of when a RiskMAP should be considered, and concludes that RiskMAPs are intended for a relatively small number of products. We believe sponsors should be clearly directed in the Guidance to state in their NDA submissions that they are either proposing a RiskMAP, or not, and why. Perhaps surprisingly, there is both reluctance and confusion on the part of sponsors around this issue, and submissions are likely to occur without an explicit statement on this matter. This will lead to confusion on the part of FDA in reviewing the submission, and difficulty within the Office of Drug Safety in providing useful feedback. A simple statement requesting the sponsor to indicate when what is proposed falls within the rubric of a RiskMAP will be helpful to all parties.

Three considerations are listed as common determinants of whether development of a RiskMAP may be desirable (lines 212-228). The three listed considerations (nature and rate of known risks vs. benefits, preventability of the event, and probability of the benefit) are important and well-stated. We strongly recommend a fourth consideration, which was raised in each of the four CERTs-sponsored invitational workshops on the theme of “benefiting the patient and managing the risk.” Distinguished leaders in government, industry, academia, and practice repeatedly identified the structure and influences of the practice environment as a critical factor...perhaps the most critical factor...in determining how practitioners will manage drug product risks. The influences of patient scheduling, for example, as manifested in time available for each patient encounter play a critical role in managing risk. Others include reimbursement influences which may deter return visits for laboratory tests, peer influences on adoption of a product with a RiskMAP, and patient or caregiver influences to prescribe a product outside the labeled indication. Indeed, in reviewing the effectiveness (or lack thereof) of black box warnings in labels or “Dear Doctor” letters, the pressures of the practice management were cited as primary reasons for these tools not reaching a threshold of effectiveness. In the earlier concept papers this was addressed through the recommendation that sponsors identify an “ideal use scenario” for any drug product that

would take into account the many influences in a practice environment that may impede ideal use. We believe this is an important consideration in both determining the need for a RiskMAP and in defining its characteristics. We encourage FDA to add a point to this section emphasizing the importance of understanding the impact of the practice environment on ultimate use of the drug product. The concept that sponsors should be able to contrast “ideal use scenario” with “likely use scenario” may be the most important point to consider in this section, and should be reinstated and emphasized.

The Guidance addresses the important tradeoff involving a risk minimization plan to improve safety, and the likely result that patients’ may have reduced accessibility to a useful drug product. The Guidance states (lines 155-156) “FDA recommends that RiskMAPs be used judiciously to minimize risks without encumbering drug availability or otherwise interfering with the delivery of product benefits to patients.” While a laudable goal, in reality this is unattainable. Any RiskMAP will inevitably encumber drug availability and interfere with the delivery of drug product benefits. Indeed, that is sometimes its purpose. The question is not whether reduction in access will occur, but how much. We suggest revised wording to capture this understanding, such as “FDA recommends that RiskMAPs be used judiciously to minimize risks without excessively encumbering drug availability or excessively ~~otherwise~~ interfering with the delivery of product benefits to patients.”

Section V. RiskMAP Evaluation: Assessing the Effectiveness of Tools and the Plan

The Guidance addresses the importance of evaluating a RiskMAP, both in aggregate as well as of the component parts. We commend FDA for making this very important point, and particularly for identifying “acceptability of RiskMAP tools by consumers and health care practitioners” (lines 464-465). Recognition of this and other behavioral factors in evaluating RiskMAPs will improve our understanding of current practices and help develop a consensus on best practices in risk management.

In the section on rationale for RiskMAP evaluation, the Guidance states that “statistical hypothesis testing...would not typically be expected”. We would suggest that FDA soften the language to “might not necessarily be expected”. While sometimes the evaluation will be a simple descriptive study, there will be times when comparisons will be useful, and indeed should be sought whenever possible (e.g., is this drug being used differently from a competitor, in a manner which is consistent with the RiskMAP?). In addition, we recommend FDA specify that statistical estimation would be expected.

In the Guidance FDA recommends that sponsors periodically “evaluate each RiskMAP tool to ensure it is materially contributing to the achievement of RiskMAP objectives or goals.” While it is important to maximize the effectiveness of all components of a RiskMAP, we should not lose sight of the fact that it is the combined effect of all elements that is most important. Section 3 and 4 emphasize the evaluation of RiskMAP tools, and while that is appropriate, we recommend FDA include wording to emphasize program effectiveness is the sine qua non of RiskMAP evaluation. If each tool is found to be individually effective, but the overall program fails to achieve its goals, that is a failure.

Related to this is the need to link RiskMAP objectives and goals (lines 551-571) with the health outcomes stated in page 5 (lines 167-173). Identifying the relationship between desired health outcomes and RiskMAP goals is critical to the long term success of RiskMAPs.

This also raises the important question of the “threshold level of risk” that will be accepted in any RiskMAP. Section III.C. Repeats the standard practice that RiskMAP goals should be stated in a way that aims to achieve maximum risk reduction, i.e., “fetal exposures to Z drug should not occur.” While this may be a true statement, it also fails to recognize we live in an imperfect world, and holds a RiskMAP to a “zero tolerance” standard that is unrealistic and will assure that all RiskMAPs will be judged to be a failure. At the very least, FDA should acknowledge this tension in the Guidance

Documents and advise sponsors to achieve consistency between how they describe RiskMAP goals that target achievement of particular health outcomes (lines 167-173) and goals of specific tools in a RiskMAP.

The Guidance describes the Agency's desire and intent to maintain a RiskMAP Web site and to provide a running commentary on particular tools in use. The summaries "will not contain information from a particular sponsor or product." While FDA believes this approach will provide an effective balance between dissemination of information and protection of proprietary information, we believe it is excessively conservative. We encourage FDA to follow the lead currently proposed in Phase IV clinical trials, to provide a central registry of individual RiskMAPs, their tools, and the assessment methods for each RiskMAP. The Agency has indicated a desire for sponsors to submit RiskMAP evaluation protocols in a manner analogous to clinical trial protocols. We believe this is a reasonable expectation, moreover we believe the submitted protocols should be in the public domain.

Although the Guidance recommends putting general information about evaluation of RiskMAPs on the Web, the document states that information on a specific product or sponsor should be shielded because of issues of confidentiality. In keeping with the precedent that post-marketing spontaneous adverse events are in the public domain, so should details of the evaluation of a RiskMAP intended to improve the balance between benefit and risk of a new product. If the actual effect of a program were different from the intended effect, that information along with the product's name should be in the public domain. If not, we are experimenting on patients without their consent, and hiding the results. The final Guidance should also strongly encourage industry to publish their evaluations.

In addition, we think the guidance should strongly urge sponsors to publish their evaluations of RiskMAPs, although we recognize that it cannot require this.

Additional Comments

Not discussed in the Guidance, but a point of concern among sponsors, practitioners, and researchers, is the question of RiskMAP consistency within a therapeutic class, calibrated by any differences in the drugs' effects. While it is reasonable to believe that drugs with similar risk/benefit profiles will have similar RiskMAPs, the Guidance Documents are silent on that issue. If the Agency believes there should be consistency in methods and approaches for drugs within a class that merit RiskMAPs, a statement to that effect would be helpful to sponsors. On the other hand, if the Agency believes, because of lack of an evidence base in developing RiskMAPs or in an effort to stimulate innovation in development of RiskMAPs, that consistency is not valued, this would be helpful information.

In addition, questions remain regarding when a RiskMAP can be terminated, and when the Agency requires review of modifications in a current RiskMAP. While the Guidance speaks to the conditions under which RiskMAPs should be considered (lines 193-228), they are silent with regard to conditions under which they can be modified and/or terminated. Inferences could be drawn that the same criteria would apply, but such inference may not be appropriate. We encourage FDA to add this important clarification to the current Guidance.

We believe that by addressing the comments and suggestions set out above, the FDA can provide more complete guidance about how to minimize the risks of drugs and biologics while maintaining their benefits.

Sincerely,

A handwritten signature in black ink, appearing to read "Robert M. Califf". The signature is written in a cursive, flowing style with a large initial "R".

Robert M. Califf, M.D.
Principal Investigator, CERTs Coordinating Center