Confirmation of Email

April 21, 2003

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Statistical Science (HFD-001)
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Dear Dr. Seligman:

We thank you for the opportunity to provide the enclosed comments on this important initiative by the Agency and on behalf of the CERTs Program we look forward to working with you in the development of these guidances.

Sincerely,

William H. Campbell, PhD, MS
Principal Investigator, UNC CERTs

Judith M. Kramer, MD, MS
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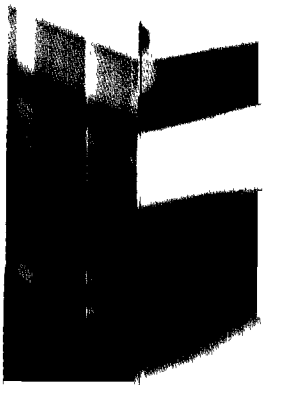
WHC/lch

Enclosures



02N-0528 Docket 02N-0528 C8

FDA Meeting
April 9-11, 2003
Comment on FDA Concept Papers: Focus on Risk Management

Bill Campbell, PhD, MS; Judith Kramer, MD, MS

We believe FDA has done an excellent job in synthesizing the current state of knowledge into a guideline on Risk Management. We are also pleased to note the document is consistent with the findings and recommendations to date of the Centers for Education on Research and Therapeutics (CERTs) series of workshops on Risk Communication, Risk Assessment, Benefit/Risk Assessment, Risk Communication and the Media, and Risk Management. Separate manuscripts will be prepared summarizing the results of each workshop, with publication scheduled for the Journal of Pharmacoepidemiology and Drug Safety.

General Points:

1. **Risk Management (or Risk Management Planning) should be seen as a continuum of activity across the complete product life cycle.**

   COMMENT: While separation of RM or RMP into distinct phases (e.g., premarketing risk assessment, risk management, pharmacovigilance) may be useful distinctions for purposes of discussion or organization of information, the creation of three separate guidances may obscure the important interrelationships of information from these different phases. Although FDA clearly states in the risk management document (lines 102-105-PDF) that "risk characterization is an ongoing process throughout a product's life cycle," the individuals using the guidance document may tend to think more in "silos" since there are 3 separate documents. At the very least, effort should be made within the text of each guidance document to link closely related concepts and activities.

2. **It is the position of CERTs that every therapeutic agent should have an individualized risk management plan and program.**

   COMMENT: CERTs applauds the use of Level I – IV to categorize a gradient for risk management programs (lines 253-260, RM Concept Paper-PDF). A standard nomenclature and taxonomy is essential to effective communication, and this taxonomy is both logical and informative. It would be useful however to define this taxonomy not just on the tools applied within each category, but more importantly according to the qualitative and quantitative level of risk that is present.

   Rather than stating (see line 122-123 RM Concept paper-PDF), "FDA anticipates that for *most* products risk management planning will be handled by the information in the PI", perhaps it should be stated that "for products *with no*

safety signal, risk management planning will be handled by the information in the PI." (italics added). If there is a safety signal, some type of active surveillance should be considered in the plan, even if a formal risk management program is not indicated.

3. **CERTs agrees with FDA that the goal of a risk management plan should be to optimize the balance of benefit-to-risk.**

   COMMENT: Since as FDA has said (line 25 RM Concept sheet) that a product is considered safe if it has a positive benefit/risk balance on a population and individual patient level, why is the definition of risk management in the document focused solely on minimizing risks (line 28) and not also on maximizing benefits while minimizing risks? Surely with some drugs, education of health professionals on proper use will also maximize benefit (e.g. through targeting of the correct patient population).

   Further, the plan/program must recognize not only the inherent benefits and risks of the product (as noted in the definition of "risk assessment" in II.A of the Concept Paper on Premarketing Risk Assessment, and II.A.C. in Risk Management Planning), but must make equal consideration of the context and conditions under which the drug will be used. This includes the type of patient and practitioner, and also the environment of practice, which includes information resources, reimbursement incentives, and barriers to communication that might impede of facilitate management of benefit/risk.

4. **Patients can play a critical role in Risk Management; indeed it is impractical to contemplate an effective Risk Management program that does not include consumers/patients in substantive ways.**

   COMMENT: Patients are an untapped resource in building effective risk management programs. Their roles should include greater responsibility for assuring effective communication at the provider/patient interface, as well as new approaches to monitoring and reporting effects of long term use. While the patient's role in risk management is implied in several points of the concept papers, it should be explicitly acknowledged and emphasized in each paper.

5. **Technology, especially information technology, offers exciting opportunities for developing new approaches to Risk Management and innovation in this area should be encouraged in sponsors' Risk Management Programs and Plans.**

   COMMENT: The potential role of PDA's is recognized in the concept papers, and it is important to recognize this technology is rapidly evolving into visual, interactive communication, and large database applications. The data of telemedicine using PDA-type devices is not far in the future, and with it will

come opportunities for innovation and creativity in managing risk. Similar opportunities will occur through inter/intranet capabilities and patient-centered electronic medical records. Risk Management should be at the cutting edge of exploring applications of these emerging technologies.

6. FDA's advice that RMP goals should be translated into pragmatic, specific, and measurable objectives will support efforts to evaluate the programs.

We commend the FDA's efforts to foster evaluation by specifying objectives.

7. Evaluation of Risk Management programs should be in the public domain.

COMMENT: It is clear the approval for marketing of new drugs involves a public trust, and the evaluation of Risk Management programs provides information needed by sponsors, providers, patients, regulators, and policy makers. CERTs strongly recommends the Agency articulate a policy that provides appropriate safeguards to sponsors for protection of legitimate proprietary interests, while at the same time assuring appropriate reporting and access to Risk Management evaluation information by communities of interests (e.g., academic researchers, practitioners, patients).

8. Risk Management must be interdisciplinary to be effective.

COMMENT: The contributions of all members of the health care team---physicians, nurses, pharmacists, allied health, and others---are essential to effectively managing risks of therapeutic agents. Just as the contributions to health care of all providers require constant innovation and evaluation to develop new models, so must risk management explore new approaches for including all providers in risk management. The CERTs Risk Series Workshops have particularly noted the need to include nurses and pharmacists in this equation.

9. The analogy of a RMP to a drug development effort is a good one; the analogy also applies to the size of the undertaking.

COMMENT: We must keep in mind that developing, pre-testing, implementation, and evaluation of a risk management program is an expensive and time-consuming venture. Furthermore, from the perspective of industry, a RMP is surely expected to limit the size of the market for the product (i.e. decreasing profit). Thus CERTs has articulated a policy issue asking the following question, "who pays/bears the burden for the design, testing, conduct, and evaluation of risk management efforts?" The RM Concept paper as written assumes that the burden is fully on industry. Is there any other alternative? Do we risk industry not developing drugs with ANY safety signal, even though the product may meet an important unmet need?

SPECIFIC COMMENTS ON CONCEPT PAPER STATEMENTS

Premarketing Risk Assessment:

1. III.F. "How can sponsors minimize medication errors" The Agency's support for proactive anticipation of problems, as illustrated with Medication Error Prevention Analysis (MEPA) should be encouraged and expanded. Not only medication errors, but all elements of the drug use process should be analyzed using Failure Mode and Effectiveness Analysis (FMEA), "what if," or similar human factor techniques. One of the key points in the CERTs Risk Series Workshops was an emphasis on proactive analysis to identify intended and unintended consequences of risk management approaches.

Risk Management Programs:

Sections I.D. (What are the goals and objectives of risk management programs?) and II.C. (How can tools be best selected or developed?) raise critically important points. In addition to supporting these sections in their entirety, CERTs would add the issue of "provider or patient burden" to the factors that must be considered in developing goals and selecting tools. A critical and difficult-to-define line must be drawn in risk management programs, one that creates barriers to access of a drug without imposing excessive restrictions on appropriate use. One of the evaluation criteria of any risk management program should be where this line occurs in practice once a risk management program is implemented.

Sections VI.B. (What information would the Goals, Objectives, and Level section contain?) and VI.C. What information would the Tools section contain?) propose excellent guidelines for developing risk management programs. To the extent possible, taking advantage of previously approved and implemented risk management programs, we would encourage greater specificity and examples in these sections.