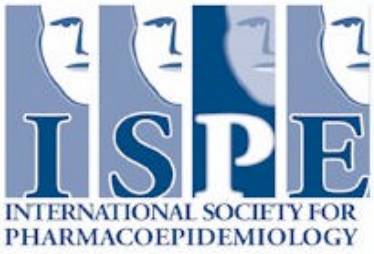

Draft Guidance for Industry Development and Use of Risk Minimization Action Plans

Docket Number [2004D-0188]

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

By the
International Society for Pharmacoepidemiology (ISPE)
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The International Society for Pharmacoepidemiology (ISPE) is very pleased to have the opportunity to offer our perspectives and suggestions, and submits for your consideration the following comments on the *Draft Guidance for Industry on Development and Use of Risk Minimization Action Plans.* We commend the Food and Drug Administration (FDA) for taking the initiative to move forward the current state of knowledge on risk management by drafting industry guidance and soliciting public comment. We thank the Agency for including many of ISPE's comments and suggestions on the 2003 concept papers. We encourage the FDA to move forward and foster further collaboration among all interested stakeholders at the Agency, sponsor(s), and other institutions. As specific applications are initiated, we strongly recommend the Agency promote discussion and collaboration among stakeholders as early as possible in the process. Finally, as an international society, we encourage international harmonization of this guidance and other FDA guidance.

About ISPE

ISPE is an international, nonprofit (501-c-3), professional membership organization dedicated to promoting pharmacoepidemiology, the science that applies epidemiological approaches to studying the use, effectiveness, values and safety of pharmaceuticals. ISPE is firmly committed to providing an unbiased scientific forum to the views of all parties with interests in drug, biologics, and devices development, delivery, use, costs and value, adverse and beneficial effects, and therapeutic risk management. Moreover, the Society provide an international forum for the open exchange of scientific information among academia, government, and industry and for the development of policy; a provider of education; and an advocate for the fields of pharmacoepidemiology and therapeutic risk management

The Society's more than 700 members represent 45 countries. ISPE members work in academic institutions, the pharmaceutical industry, government agencies, and non-profit and for-profit private organizations. ISPE members are researchers with background and training in epidemiology, biostatistics, medicine, public health, nursing, pharmacology, pharmacy, law, and health economics.

Our comments are based on a careful review of the draft guidance by the Society's membership at-large as well as by ISPE Fellows, members of the Board of Directors and Executive Committee and past presidents.

General Comments

ISPE is very pleased that substantial revisions have been made to the previous concept paper. We applaud the FDA for appropriately considering that risk must always be viewed in the context of benefits achieved by patients from access to treatment options. The recognition noted throughout the document of this important balance between benefit and risk places the Risk Minimization Action Plans (RiskMAPs) into a more appropriate context than the prior concept paper. We are also pleased with the deletion of the

specified levels of risk minimization action plans. The new document instead focuses on targets and modes of interventions, a change which provides more helpful guidance to sponsors as they consider risk minimization tools. The new document also offers guidance on the process of developing and submitting RiskMAPs and for interacting with FDA, which is particularly helpful.

The document is clear in structure. The coordinated introduction across all three guidance documents, cross-referencing to the other documents, and better coordination of content across the documents is another modification made since the initial concept paper. These changes improve the coherence and usefulness of the series of guidance documents.

The guidance places appropriate emphasis on evaluating the impact of RiskMAPs. In so doing, it acknowledges the fact that there is only limited experience with these evaluations. There is some literature and experience relating to risk minimization tools and program evaluation methods. Explicit citation of these methods via references to publicly available information would provide a useful service to organizations considering risk minimization programs in the future. A serious limitation in sharing experience, however, is that some of the information and experience that would be most useful to sponsors is embargoed by publication or covered in the confidentiality between company and Agency, yet it would be of great benefit in advancing the science or Risk Management and in expanding the Risk Management tool box.

Our greatest area of concern is the assertion that RiskMAPs would be considered only in very limited circumstances. It is ISPE's view that all therapeutics require systematic monitoring of utilization and safety throughout their lifecycle. All three guidance documents refer to risk management as a 4-part iterative process of "(1) assessing a product's risk-benefit balance, (2) developing and implementing tools to minimize its risks while preserving its benefits, (3) evaluating tool effectiveness and reassessing the risk-benefit balance, and (4) making adjustments, as appropriate, to the risk minimization tools to further improve the benefit-risk balance." However, absent a Pharmacovigilance Plan (PVP) for all products, which would provide the framework for this monitoring, there is a gap between routine safety surveillance and the therapeutics, which "pose an unusual type or level of risk." We suggest that the solution is to expect a PVP for all new products, which would be consistent with international harmonization efforts (ICH – E2E guidelines). If the PVP becomes universal practice, then formal RiskMAPs can be restricted to the "unusual" cases.

ISPE believes there is still a great deal of work to be done in the development and refinement of analytic methods for evaluating safety signals as well as methods for risk assessment and risk management evaluation. ISPE is committed to working with the FDA and others such as the CERTs (Centers for Education and Research on Therapeutics) to further knowledge of the methodological and statistical techniques required. We are firmly committed to providing an unbiased scientific forum to the views of all parties with interests in the safety of therapeutics, and as such are deeply committed to the advancement of Risk Management Sciences.

Specific Comments

Section: I. Introduction

Line(s)	Comment
2	Consider the term "risk reduction" rather than "risk minimization" We are pleased with the new terminology, which is an important improvement over "risk management plan" from the prior concept paper. However, consider that term "minimization" implies that other factors, such as benefits and costs, are irrelevant. The term "reduction" is a more accurate word to describe the intent in this guidance, which seeks to reduce a product's risk "while preserving its benefits."

Section: II. Background

Line(s)	Comment
56-57	Consider including risk communication in addition to risk assessment and risk minimization
61-63	Clarify that this framework of program evaluation and continuous improvement is not without precedent. Frameworks for continuous quality improvement have been developed and applied in many fields (e.g., transportation and environmental risk reduction, manufacturing). Indeed, the Draft guidance on Pre-marketing Risk Assessment refers to Failure Mode and Effect Analysis (FMEA). While a single framework has not been identified as the optimal model for therapeutic risk management, readers may not be aware of the extensive experience with and literature in this area and would benefit from such reference.
77	Define "unusual" The term "unusual" is not very specific and we either need to explain what it is or use a term that would provide more information about what we are looking for; as an example: events that have not been previously documented, event rates higher than expected, different rates in different populations etc.

Section: IIII. The Role of Risk Minimization and RiskMAPs in Risk Management

Line(s)	Comment
121-126	This comprehensive definition of safety is excellent and should be used more frequently throughout these and other documents.
121-126	Perhaps the concept of risk tolerance should be explored to describe the level of risk taken in return for potential benefits. Since risk-benefit ratios are numerically misleading if we do not know what the risks and benefits are, nor the values of each to patients, these need to be better defined and delineated in risk-benefit assessments. As an example, benefits of reduced pain versus risks for mild gastric upset are not the same as benefits of improved sexual function versus the risk of a cardiac event. Tolerance would incorporate the concept of utility assessment. Consider adding the concept of tolerance, preference, or acceptability of the risks compared to benefits in this section.
128-138	Add "patient preferences" after "existing therapeutic options" on line 136. This is an excellent section depicting the complexities associated with balancing risks and benefits. The one missing element from this discussion is the perspective of patients. The comments above, relating to tolerance, could also be addressed in this paragraph.
143-150	Little guidance has been provided on what constitutes "routine risk minimization measures," and the other draft guidance documents do not address this point. The ongoing 4-part risk management process described in each of the guidance documents culminates in the review and potential revision of the product label. Such assessment must also consider adherence to the label. Adherence can and should be assessed through therapeutic utilization studies. Revise to read (suggestions in caps): "FDA believes that, for most products, routine risk minimization measures are sufficient. Such measures involve, for example, FDA-approved professional labelling describing the conditions in which the drug can be used safely and effectively, updated from time to time to incorporate information from post marketing surveillance or CLINICAL STUDIES AND EPIDEMIOLOGY studies, INCLUDING PATIENT CHARACTERIZATION AND THERAPEUTIC UTILIZATION STUDIES revealing new benefits (e.g., new indications or formulations), risk concerns, AND ADHERENCE TO LABEL RECOMMENDATIONS. IT IS IN THE INTEREST OF PATIENTS, SPONSORS AND FDA TO FURTHER OUR KNOWLEDGE ABOUT THE EFFECTIVENESS OF LABELING AS A RISK MANAGEMENT TOOL."

147-151	We appreciate the important role of the product label and the efforts of FDA to enhance its clarity and relevance. However, because the product label itself is recognized as insufficient as a tool to guide prescribing behaviour and patient adherence, the term "cornerstone" seems out of place. Perhaps the paragraph could refer instead to the process of risk management, which culminates in the review and revision of the product label.
162-183	It is useful to employ the concept of two levels of goals, one idealistic and one pragmatic. However, the terms "goals" and "objectives" are synonyms, even though they are often used to reflect different levels of goals in the context of organizational management. To avoid any confusion, we urge greater clarity in the terminology. We suggest using the terms "idealized goals" and "programmatic objectives" throughout.
175-183	The example does not present measurable objectives. For example, "guiding physician prescribing practices and/or pharmacist dispensing practices" are tools rather than objectives. We suggest giving an example of a measurable objective, such as the % of physicians who report knowledge of the dangers of concomitant prescribing.
195-198	Use of "routine safety surveillance" is insufficient to identify some risks that may warrant a RiskMAP. The recommendation made earlier of adopting the Pharmacovigilance Plan (PVP) process for all new products would address this concern.
195-228	Provide additional information on how to identify issues that may need a RiskMAP considering the mechanism of the event, whether the basis is pharmacologic or idiosyncratic, whether the event is dose-related or not-dose-related, the incidence of the event, predispositions in target population, potential for misuse or abuse, similarity to available agent and whether it has a RiskMAP. Also consider, the role that pharmacogenomics can play in identifying patient at risk or identifying patient unlikely to benefit. Medication errors and patient compliance should also be taken into consideration. FDA can assist sponsors in identifying when to consider a RiskMAP based on these assessments. While the other guidance documents consider elements of risk assessment in greater detail, it is perhaps worth expanding this section in the event the document is used as a stand-alone guidance.
201	Add "and data on actual utilization patterns" as substitute for "use." Determination of the risk-benefit profile of a product in actual use cannot be made without an understanding of the extent to which real world utilization differs significantly from the intended use.

Section: IV. Tools for Achieving RiskMAPs Goals and Objectives

Line(s)	Comment
260-265	When possible, consider using a step-wise approach with the first step being a Letter to Health professionals, introduction of patient package inserts and prominent public notification. The stepwise approach is consistent with the philosophy of using least burdensome strategy possible.
347-437	Provide reference to information in the public domain about tools and experience with tools. Some literature exists on the effectiveness of various risk minimization tools. As mentioned in our general comments, some reference to the literature would be helpful as organizations consider the selection tools to address specific product issues. Since this literature should evolve over time, an option would be to provide an up-to-date reference list on the web site that is mentioned on line 347.
	ISPE appreciates the amount and type of guidance included in this section, and the sensitivity to potential unintended consequences of risk minimization tools. It is important to use "tools with the least burdensome effect on health care practitioner-patient, pharmacist-patient, and/or other health care relationships."
373	We suggest a definition for "adequate" be provided. As used in this sentence, "adequate risk minimization" is vague. Adequacy could be identified in terms of the program objectives aimed at the idealized goal for risk reduction.
389-397	Consider including a statement (new #5) about making tools available to each market and tailored as necessary based on available technology, culture, etc.
466	Add "both in the short-term and long-term" at the end of the sentence after "(3) compliance with important RiskMAP processes or procedures." Compliance with risk minimization tools can be expected to vary over time (increasing or decreasing) as healthcare professionals and patients become more familiar with the product and the RiskMAP processes.

Line(s)	Comment
485	Whenever possible, it would be preferable to measure outcomes and prescribing behaviour rather than knowledge. However, there may be

	circumstances when surveys of knowledge may be an appropriate program objective.
488	After "Ideally, the chosen measure would directly measure the RiskMAP's health outcome goal." Add the following sentence: " Selection of the measure should take into account any existing knowledge of the background or expected frequency of the outcome, event, process, knowledge, or behaviour in the absence of the RiskMAP tool."
492-493	Add: The validity of the surrogate markers must be demonstrated independently of the intervention.
502-508	In the assessment of the validity of outcomes, the concept of sensitivity, specificity, positive and negative predictive values should be stated as quantitative measures of validity.
516-518	Consider acknowledging that there remains a role for reviewing spontaneous adverse event data to help assess the effectiveness of RiskMAPs. Although it is true that the use of spontaneous adverse event data to identify outcomes is limited by under-reporting, such data are still very useful. There are methods, which allow us to model the confidence intervals around the risk estimate and determine whether the acceptable threshold is included. Furthermore, they are truly population-based. The differential under-reporting rate that would occur pre- and post-implementation of a RiskMAP would introduce a bias that would lead to a conservative estimate of the effectiveness of the RiskMAP. After the implementation of a RiskMAP, physicians may become more aware of the risk associated with the drug, and therefore will be more likely to report adverse events. This would therefore produce a conservative estimate of the effectiveness of the tool.
522-530	When other circumstances are similar (e.g., risk minimization tools, product indication), robust data might be available in other settings, such as countries that offer universal access to healthcare.
14; 553-571	It is important to have a systematic approach to reviewing the overall RiskMAP and not just the individual components. Such an approach can better guide decisions about changes needed to individual tools that form the overall RiskMAP. Program Evaluation and/or Continuous Quality Improvement processes are standard methods in other fields, including the manufacturing of medical products that can be applied to the evaluation of RiskMAPs. We therefore suggest adding a paragraph at end: "A systematic program evaluation model, such as Failure Modes and Effect Analysis (FMEA), can provide a framework for evaluating the individual components of a RiskMAP and the relative importance of adherence to each in achieving the overall idealized goal of the RiskMAP."

573 -603	As testing a tool before implementation may be impossible or unethical, simulated cohorts may be assembled and the effects of different intervention estimated. Consider adding new sentence at lLine 588: "Simulation techniques in advance of implementation may be useful and can provide a benchmark for subsequent program evaluation."
573-603	References to literature on the effectiveness of tools should be included, as mentioned earlier under Section IV D.
573-603	We support the recommendation of pre-testing. More specific guidance can be included. Designs for pre-testing should be suggested. Examples include pre-post test with comparable or non-comparable control group; for larger scale programs, interrupted time series. Advantages and limitations of each, and key references should be included.

Section: VI. Communicating With FDA Regarding RiskMAP Development and Design Issues

Line(s)	Comment
629-674	This section might include some distinction between the communication of "unusual" and "routine" risk minimization activities. Consider specifying that if the risk appears to be high, the notification to FDA should be immediate. If the risk is not high, and company-initiated risk minimization activities have been ongoing, notification might occur through the Periodic Safety Update Reports.
629-674	Consider mentioning that a sponsor may request that the Office of Drug Safety (ODS) be included in early discussion with the sponsor on potential RiskMAPs. Currently sponsors may receive different views of risk assessment and RiskMAPs from different offices within FDA. It is particularly important to have coordinated views within FDA to assure the most appropriate RiskMAP options are considered and selected. Because regular communication with sponsors is guided by the product's review division, some sponsors may be unaware that they can request involvement by ODS at an early stage of discussion.

Section: VII. Recommended Elements of a RiskMAP Submission to FDA

Line(s)	Comment
816	We support the recommendation that analytical plans address the issues

	mentioned in the document. Nevertheless, the phrase "since RiskMAP evaluations will often rely upon observational data" implies that the observational nature of the study makes paying attention to these matters more relevant. Attention to the topics described in the document (with the exception of bias) is equally relevant whether a study is experimental or nonexperimental. Delete "Since RiskMAP evaluations will often rely upon observational data," and begin the sentence with "We recommend that the analytical plan…"
818	We strongly support and encourage the Agency's endorsement of the use of confidence intervals. The agency should also emphasize that confidence intervals should not be used as surrogate significance tests, merely to determine whether the null value falls within the interval. It is never appropriate to interpret a confidence interval in this way, but it is particularly egregious in safety evaluations, because it encourages the common misinterpreta tion that a "nonsignificant" result implies the absence of an effect.
20; 838	Amend the sentence to: "In general the sponsor **will be** expected to propose modifications to the RiskMAP if the RiskMAP goals were not achieved" The sentence "in some cases the sponsor may choose to propose modifications to the RiskMAP if the RiskMAP goals were not achieved" seems too "soft". FDA already states (page 2 of the same guidelines; line 61) that "[risk management] should be continuous… with the results of the risk assessment informing the sponsor' decisions regarding risk minimization". It would be difficult to imagine a situation where the sponsor "may not choose" to modify the goals of a RiskMAP if its goals were not achieved.

Concluding Comments

ISPE is committed to providing an unbiased scientific forum to consider the views of all parties with interests in the safety of therapeuticals, and as such is deeply committed to the advancement of risk management science generally and this proposed industry guidance specifically.

The Society welcomes the opportunity for further collaboration with the FDA and its Centers on risk management and other related initiatives.