Guidance for Industry

Development and Use of Risk Minimization Action Plans

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact (CDER) Christine Bechtel at 301-443-5572, or (CBER) Mark Weinstein at 301-827-3518.

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)

May 2004
Clinical Medical

Guidance for Industry

Development and Use of Risk Minimization Action Plans

Additional copies are available from:

Office of Training and Communication
Division of Drug Information, HFD-240
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857
(Tel) 301-827-4573
http://www.fda.gov/cder/guidance/index.htm

or

Office of Communication, Training, and
Manufacturers Assistance, HFM-40
Center for Biologics Evaluation and Research
Food and Drug Administration
1401 Rockville Pike, Rockville, MD 20852-1448
http://www.fda.gov/cber/guidelines.htm.
(Tel) Voice Information System at 800-835-4709 or 301-827-1800

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)

May 2004
Clinical Medical

TABLE OF CONTENTS

Guidance for Industry[1]
Development and Use of Risk Minimization Action Plans

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This document provides guidance to industry on the development, implementation, and evaluation of risk minimization action plans for prescription drug products, including biological drug products.[2] In particular, it gives guidance on (1) initiating and designing plans to minimize known risks (i.e., risk minimization action plans or RiskMAPs), (2) selecting and developing tools to minimize those risks, (3) evaluating and monitoring tools and RiskMAPs, and (4) the recommended components of a RiskMAP submission to FDA.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

A. PDUFA III's Risk Management Guidance Goal

[1] This guidance has been prepared by the PDUFA III Risk Management Working Group, which includes members from the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration (FDA).

[2] For ease of reference, this guidance uses the term *product* or *drug* to refer to all drug products (excluding blood and blood components) regulated by CDER or CBER. Similarly, for ease of reference, this guidance uses the term *approval* to refer to both drug approval and biologic licensure.

Paperwork Reduction Act Public Burden Statement: This guidance contains information collection provisions that are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (PRA) (44 U.S.C. 3501-3520). The collection(s) of information in this guidance were approved under OMB Control No. 0910-0001 (until March 31, 2005) and 0910-0338 (until August 31, 2005).

On June 12, 2002, Congress reauthorized, for the second time, the Prescription Drug User Fee Act (PDUFA III). In the context of PDUFA III, FDA agreed to satisfy certain performance goals. One of those goals was to produce guidance for industry on risk management activities for drug and biological products. As an initial step towards satisfying that goal, FDA sought public comment on risk management. Specifically, FDA issued three concept papers. Each paper focused on one aspect of risk management, including (1) conducting premarketing risk assessment, (2) developing and implementing risk minimization tools, and (3) performing postmarketing pharmacovigilance and pharmacoepidemiologic assessments. In addition to receiving numerous written comments regarding the three concept papers, FDA held a public workshop on April 9–11, 2003, to discuss the concept papers. FDA considered all of the comments received in producing three draft guidance documents on risk management activities:

1. *Premarketing Risk Assessment (Premarketing Guidance)*
2. *Development and Use of Risk Minimization Action Plans (RiskMAP Guidance)*
3. *Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment (Pharmacovigilance Guidance)*

B. Overview of the Risk Management Draft Guidance Documents

Like the concept papers that preceded them, each of the three draft guidance documents focuses on one aspect of risk management. The *Premarketing Guidance* and the *Pharmacovigilance Guidance* focus on premarketing and postmarketing risk assessment, respectively. The *RiskMAP Guidance* focuses on risk minimization. Together, risk assessment and risk minimization form what FDA calls *risk management*. Specifically, risk management is an iterative process of (1) assessing a product's benefit-risk balance, (2) developing and implementing tools to minimize its risks while preserving its benefits, (3) evaluating tool effectiveness and reassessing the benefit-risk balance, and (4) making adjustments, as appropriate, to the risk minimization tools to further improve the benefit-risk balance. This four-part process should be continuous throughout a product's lifecycle, with the results of risk assessment informing the sponsor's decisions regarding risk minimization.

When reviewing the recommendations provided in this guidance, sponsors and applicants should keep the following points in mind:

- Many recommendations in this guidance are ***not*** intended to be generally applicable to all products.

  Industry already performs risk assessment and risk minimization activities for products during development and marketing. The Federal Food, Drug, and Cosmetic Act (FDCA) and FDA implementing regulations establish requirements for ***routine*** risk assessment and risk minimization (e.g., FDCA section 503(b) (21 U.S.C. 353(b)), which provides for limiting drugs to prescription status; FDA regulations regarding spontaneous adverse event reporting and FDA-approved professional labeling). As a result, many of the recommendations presented here focus on situations when a product may pose an unusual type or level of risk. To the extent possible, we have specified in the text whether a recommendation is intended to apply to all products or only this subset of products.

- It is of critical importance to protect patients and their privacy during the generation of safety data and the development of risk minimization action plans.

  During all risk assessment and risk minimization activities, sponsors must comply with applicable regulatory requirements involving human subjects research and patient privacy.[3] FDA recommends that sponsors comply with ethical principles for patient protection.

- To the extent possible, this guidance conforms with FDA's commitment to harmonize international definitions and standards as applicable.

  The topics covered in this guidance are being discussed in a variety of international forums. We are participating in these discussions and believe that, to the extent possible, the recommendations in this guidance reflect current thinking on related issues.

- When planning risk assessment and risk minimization activities, sponsors should consider stakeholder input (e.g., from consumers, pharmacists, physicians, third-party payers).

- There are points of overlap among the three guidances.

  We have tried to note in the text of each guidance when areas of overlap occur and when referencing one of the other guidances might be useful.

III. THE ROLE OF RISK MINIMIZATION AND RISKMAPS IN RISK MANAGEMENT

As described above, FDA views risk management as an iterative process encompassing both risk assessment and risk minimization. In particular, the premarketing guidance and the pharmacovigilance guidance discuss how sponsors should engage in evidence-based risk assessment for all products in development and on the market. Evidence-based risk assessment will assist the sponsor in defining the nature and extent of a product's risks in relation to its benefits. The goal of risk minimization is to minimize a product's risks while preserving its benefits. For the majority of products, routine risk minimization measures are sufficient to minimize risks and preserve benefits. Only a few products are likely to merit consideration for additional risk minimization efforts (see section III.D.).

[3] See 45 CFR part 46 and 21 CFR parts 50 and 56. See also the Health Insurance Portability and Accountability Act of 1996 (HIPAA) (Public Law 104-191) and the Standards for Privacy of Individually Identifiable Health Information (the Privacy Rule) (45 CFR part 160 and subparts A and E of part 164). The Privacy Rule specifically permits covered entities to report adverse events and other information related to the quality, effectiveness, and safety of FDA-regulated products both to manufacturers and directly to FDA (45 CFR 164.512(b)(1)(i) and (iii) and 45 CFR 164.512(a)(1)). For additional guidance on patient privacy protection, see http://www.hhs.gov/ocr/hipaa.

A. Relationship Between a Product's Benefits and Risks

The statutory standard for FDA approval of a product is that the product is safe and effective for its labeled indications under its labeled conditions of use (see sections 201(p)(1) and 505(d) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321(p)(1) and 355(d)). FDA's determination that a product is safe, however, does not suggest an absence of risk. Rather, a product is considered to be safe if the clinical significance and probability of its beneficial effects outweigh the likelihood and medical importance of its harmful or undesirable effects. In other words, a product is considered safe if it has an appropriate benefit-risk balance for the intended population and use.

Benefit and risk information emerges continually throughout a product's lifecycle (i.e., during the investigational and marketing phases) and can reflect the results of both labeled and off-label uses. Benefits and risks can result in a range of corresponding positive and negative effects on patient outcomes that may (1) be cosmetic, symptomatic, or curative; (2) alter the course of the disease; or (3) affect mortality. A major difficulty in relating benefits and risks is that they are usually measured in different units. Thus, one often needs to compare a modest benefit that occurs in many patients with a rare but very serious adverse effect. Benefits as well as risks are also patient-specific and are influenced by such factors as the severity of the disease being treated, its outcome if untreated, existing therapeutic options, and the intended patient population. Thus, assessment and comparison of a product's benefits and risks is a complicated process that is influenced by a wide range of individualized factors.

B. Determining an Appropriate Risk Minimization Approach

To help ensure safe and effective use of their products, sponsors have always sought to maximize benefits and minimize risks. FDA believes that, for most products, routine risk minimization measures are sufficient. Such measures involve, for example, FDA-approved professional labeling describing the conditions in which the drug can be used safely and effectively, updated from time to time to incorporate information from postmarketing surveillance or studies revealing new benefits (e.g., new indications or formulations) or risk concerns. Efforts to make FDA-approved professional labeling clearer, more concise, and better focused on information of clinical relevance reflect the Agency's belief that such labeling is the cornerstone of risk management efforts for prescription drugs. [4] For most products, routine risk management will be sufficient and a RiskMAP need not be considered.

For the small number of products where a RiskMAP should be considered (see section III.D.), sponsors are encouraged to consider developing a RiskMAP. 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.

This guidance focuses on the development, implementation, and evaluation of RiskMAPs.

[4] For example, see the Proposed Rule on Requirements on Content and Format of Labeling for Human Prescription Drugs and Biologics; Requirements for Prescription Drug Product Labels that published in the *Federal Register* on December 22, 2000 (65 FR 81081).

C. Definition of Risk Minimization Action Plan (RiskMAP)

As used in this document, the term RiskMAP means a strategic safety program designed to meet specific *goals* and *objectives* in minimizing known risks of a product while preserving its benefits. A RiskMAP targets one or more safety-related health outcomes or goals and uses one or more *tools* to achieve those goals.[5]

FDA recommends that RiskMAP goals target the achievement of particular health outcomes related to known safety risks. FDA suggests that sponsors state goals in a way that aims to achieve maximum risk reduction. The following are examples of RiskMAP goals: "patients on X drug should not also be prescribed Y drug" or "fetal exposures to Z drug should not occur." FDA recommends that goals be stated in absolute terms. Although it might not be possible to ensure that absolutely no one on X drug receives Y drug, FDA believes that a *goal*, as the term implies, should reflect the ideal outcome of a RiskMAP.

FDA recommends that RiskMAP goals be translated into pragmatic, specific, and measurable program *objectives* that result in processes or behaviors leading to achievement of the RiskMAP goals. Objectives can be thought of as intermediate steps to achieving the overall RiskMAP goal. A RiskMAP goal can be translated into different objectives, depending upon the frequency, type, and severity of the specific risk or risks being minimized. For example, objectives to achieve a goal of eliminating dangerous concomitant prescribing could include guiding physician prescribing practices and/or pharmacist dispensing practices. As described in greater detail in section IV., many processes or systems to minimize known safety risks are available or under development for use in RiskMAPs. These systems include:

- targeted education and outreach for health care practitioners or patients
- reminder systems, processes, or forms to foster reduced-risk prescribing and use
- performance-linked access systems that guide prescribing, dispensing, and use of the product to target the population and conditions of use most likely to confer benefits and to minimize particular risks

D. Determining When a RiskMAP Should Be Considered[6]

[5] Although all products with RiskMAPs would also have FDA-approved professional labeling, the term *tool* as used in this document means a risk minimization action in addition to routine risk minimization measures. Some tools may be incorporated into a product's FDA-approved labeling, such as medication guides or patient package inserts. As used in this document, the FDA-approved professional labeling refers to that portion of approved labeling that is directed to a health care practitioner audience. See section IV for a more detailed discussion of other non-routine risk minimization tools that focus on targeted education and outreach.

[6] For the most part, this guidance directs its recommendations to sponsors of innovator products. However, FDA recognizes that a generic product may have the same or similar benefit-risk balance as the innovator and may, therefore, be an appropriate candidate for consideration of a RiskMAP.

As described in the premarketing guidance and pharmacovigilance guidance, evidence-based risk identification, assessment, and characterization are processes that continue throughout a product's lifecycle. Therefore, a risk warranting the consideration of a RiskMAP could emerge during premarketing or postmarketing risk assessment.[7] The Agency recommends that the appropriate information for consideration in making such a determination include, as applicable, (1) data from the clinical development program, postmarketing surveillance, and phase 4 studies, and (2) the product's intended population and use.

FDA may recommend that a sponsor consider a RiskMAP based on the Agency's own interpretation of risk information.

As discussed above, the relationship between a product's risks and benefits is complicated and multi-faceted. As a result, it is not straightforward to assess a product's risks and benefits in specific subgroups or circumstances. Decisions to develop, submit, or implement a RiskMAP are always made on a case-by-case basis, but several considerations are common to most determinations of whether development of a RiskMAP may be desirable:

- Nature and rate of known risks versus benefits: Comparing the characteristics of the product's adverse events with those of the product's benefits may help clarify whether a RiskMAP could improve the product's benefit-risk balance. The characteristics to be weighed might include the (1) types, magnitude, and frequency of risks and benefits, (2) populations at greatest risk and/or those likely to derive the most benefit, (3) existence of treatment alternatives, and (4) reversibility of adverse events observed.

- Preventability of the event: Serious and labeled adverse events that can be minimized or avoided by preventive measures are the preferred candidates for RiskMAPs.

- Probability of benefit: If factors are identified that can predict effectiveness, a RiskMAP could help encourage use accordingly to increase benefits relative to known risks.

For example, opiate drug products have important benefits in alleviating pain but are associated with significant risk of overdose, abuse, and addiction. The Agency recommends that sponsors of Schedule II controlled substances, including Schedule II extended release or high concentration opiate drug products, consider developing RiskMAPs for these products.

IV. TOOLS FOR ACHIEVING RISKMAP GOALS AND OBJECTIVES

A risk minimization tool is a process or system intended to minimize known safety risks. When risks are minimized, the benefit-risk balance is more likely to be favorable. When the conditions in which a product can be used safely and effectively are well-defined, use of the product under those conditions is more likely.

Tools can communicate particular information regarding optimal product use and can also provide guidance on prescribing, dispensing, and/or using a product in the most appropriate

[7] See section VII for a detailed discussion of RiskMAP submissions.

situations or patient populations. A number of tools are available, one or more of which could be used in the minimization of product risk. FDA encourages and anticipates the development of additional tools.

A. Relationship of RiskMAP Tools to Objectives and Goals

Risk minimization tools are designed to help achieve one or more RiskMAP objectives that serve the overall RiskMAP goal or goals. One or more tools can be chosen to achieve a particular objective. For example, a sample goal might be that patients with condition A should not be exposed to product B. An objective for achieving this goal might be to communicate to patients that if they have condition A, they should not take product B. Depending on the likelihood and severity of the adverse event associated with product B in a patient with condition A, a variety of tools could be applied to achieve this objective. One possible tool would be patient labeling explaining that a patient with condition A should not take product B. On the other hand, if the potential harm to a patient with condition A is severe and/or likely to occur, a more active tool may be appropriate. For example, the sponsor could choose to develop a patient agreement where the patient actually acknowledges, before receiving the product, that he or she knows that product B should not be taken if he or she has condition A.

B. Categories of RiskMAP Tools

A variety of tools are currently used in risk minimization plans. These fall within three categories: (1) targeted education and outreach, (2) reminder systems, and (3) performance-linked access systems. A RiskMAP might include tools from one or more categories, depending on its risk minimization goals. FDA notes that a sponsor's selection of specific categories of tools for a drug product should not be used in an assessment of comparative safety to another drug product without a RiskMAP or with a different RiskMAP.

1. Targeted Education and Outreach

FDA recommends that sponsors consider tools in the targeted education and outreach category (1) when product risks cannot be minimized with routine risk minimization measures alone or (2) as a component of RiskMAPs using reminder or performance-linked access systems (see sections IV.B.2. and 3. below).

Tools in this category employ specific, targeted education and outreach efforts to increase appropriate knowledge of key people or groups (e.g., health care practitioners and consumers) that have the capacity to prevent or mitigate the product risks of concern.[8] Examples of tools in this category are as follows:

- health care practitioner letters
- training programs for health care practitioners or patients
- Continuing Education (CE) for health care practitioners

[8] This guidance is not intended to have any effect on preemption under the FDCA and FDA implementing regulations of state-law actions relating to risk communications for drugs.

- prominent professional or public notifications
- patient labeling such as medication guides and patient package inserts
- focused or limited promotional techniques such as product sampling or direct-to-consumer advertising

In addition to informing health care practitioners and patients about conditions of use contributing to product risk, educational tools can inform them of conditions of use that are important to achieve the product's benefits. For example, a patient who takes a product according to labeled instructions is more likely to achieve maximum product effectiveness. On the other hand, deviations from the labeled dose, frequency of dosing, storage conditions, or other labeled conditions of use might compromise the benefit achieved, yet still expose the patient to product-related risks. Risks and benefits can have different dose-response relationships. Risks can persist and even exceed benefits when products are used in ways that minimize effectiveness. Therefore, educational tools can be used to explain how to use products in ways that both maximize benefits and minimize risks.

2. Reminder Systems

We recommend that tools in the reminder systems category be used in addition to tools in the targeted education and outreach category when targeted education and outreach tools are insufficient to minimize those risks.

Tools in this category include systems that prompt, remind, double-check or otherwise guide health care practitioners and/or patients in prescribing, dispensing, or receiving a product in ways that minimize risk. Examples of tools in this category are as follows:

- patient agreement or acknowledgment forms
- certification programs for practitioners (i.e., when physicians complete training and demonstrate knowledge and understanding)
- enrollment of physicians, pharmacies, and/or patients in special educational programs that reinforce appropriate product use
- limited amount in any single prescription or refill of product
- specialized product packaging to enhance safety
- specialized systems or records that attest to safety measures having been satisfied (e.g., prescription stickers, physician attestation of capabilities)

3. Performance-Linked Access Systems

Performance-linked access systems include systems that link product access to laboratory testing results or other documentation. FDA recommends that tools in this category be used when (1) products have significant or otherwise unique benefits in a particular patient group or condition,

but unusual risks also exist, such as irreversible disability or death, and (2) routine risk minimization measures, targeted education and outreach tools, and reminder systems are insufficient to minimize those risks.

Examples of tools in this category include:

- the sponsor's use of compulsory reminder systems, as described in the previous section (i.e., the product is not made available unless there is an acknowledgment, certification, enrollment, or appropriate test records)
- prescription only by specially certified health care practitioners
- product dispensing only by specially certified pharmacies or practitioners
- product dispensing only to patients with evidence or other documentation of safe-use conditions (e.g., lab test results)

C. Description of RiskMAP Tools

FDA plans to develop a RiskMAP Web site that will include (1) descriptions of tools that are currently used in RiskMAPs and (2) other information relevant to RiskMAP development (see section IV.D. below). The information will be made available consistent with federal law and regulations governing disclosure of information by FDA to the public. The list of tools will be intended to assist sponsors in designing a RiskMAP but will not suggest that the listed tools are FDA-approved or -validated. To the contrary, FDA does not suggest that the tools listed on the Web site are the only tools and encourages sponsors to develop tools that may be optimal for their particular products.

D. Selecting and Developing the Best Tools

Given the variety of available tools, FDA recommends that a sponsor carefully consider which tool or tools are most appropriate, given the goals and objectives of its product's RiskMAP. A tool could be developed or selected based on its individual impact and/or because of its impact when used in coordination with other tools. Generally, the best tools would be those that have a high likelihood of achieving their objective based on positive performance in other RiskMAPs or in similar settings and populations. Relevant non-RiskMAP evidence and experience can be found in health care quality initiatives, public health education and outreach, marketing, and other outcomes-based research (see section V. for a more detailed discussion of evaluating tools' effectiveness).

Although FDA suggests that the best tool or tools be selected on a case-by-case basis, the following are generally applicable considerations in designing a RiskMAP. In choosing tools for a RiskMAP, FDA recommends that sponsors:

- Maintain the widest possible access to the product with the least burden to the health care system that is compatible with adequate risk minimization (e.g., a reminder system tool should not be used if targeted education would likely be sufficient).

- Identify the key groups who have the capacity to minimize the product's risks (such as physicians, pharmacists, patients, and third-party payers) and define the anticipated role of each group.

- Seek input from the aforementioned groups on the feasibility of implementing and accepting the tool in usual health care practices, disease conditions, or lifestyles. Examples of considerations could include (but would not be limited to) patient and health care practitioner autonomy, time effectiveness, economic issues, and technological feasibility.

- Acknowledge the importance of using tools with the least burdensome effect on health care practitioner-patient, pharmacist-patient, and/or other health care relationships.

- Design the RiskMAP to be:

    1. compatible with current technology

    2. applicable to both outpatient and inpatient use, as appropriate

    3. accessible to patients in diverse locales, including non-urban settings

    4. consistent with existing tools and programs that have achieved positive results

- Select tools based on available evidence of effectiveness in achieving the specified objective (e.g., tools effectively used in pregnancy prevention).

- Consider indirect evidence of tool effectiveness in a related area that supports the rationale, design, or method of use (e.g., tools applied in modifying patient or health care practitioner behaviors in medical care settings).

- Consider, and seek to avoid, unintended consequences of tool implementation that obstruct risk minimization and product benefit.

FDA recognizes that, once it approves a product for marketing, health care practitioners are the most important managers of product risks. FDA believes that, by including in the FDA-approved professional labeling information on the conditions in which medical products can be used safety and effectively by their intended population and for their intended use or uses, the Agency and the sponsor encourage health care practitioners to prescribe medical products in circumstances that yield a favorable benefit-risk balance. However, as the Agency has long recognized, the FDCA and FDA regulations establish requirements governing the safety and effectiveness of medical products. FDA does not have authority under these provisions to control decisions made by qualified health care practitioners to prescribe products for conditions

other than those described in FDA-approved professional labeling, or to otherwise regulate medical or surgical practice. FDA believes that, in designing RiskMAPs, sponsors should recognize the central role played by health care practitioners in controlling the risks of medical product use and should adopt tools that facilitate this role.

E. Mechanisms Available to the FDA to Minimize Risks

This guidance focuses on the tools that industry can incorporate into RiskMAPs. As noted, FDA has a variety of risk management measures at its disposal under the FDCA and FDA regulations (e.g., prescription designation, FDA-approved professional labeling). FDA must occasionally invoke other mechanisms to minimize the risks from medical products that pose serious risks to the public health. These tools include:

- FDA-requested product recalls, warning and untitled letters, and import alerts
- safety alerts, guidance documents, and regulations
- judicial enforcement procedures such as seizures or injunctions

Further information on these mechanisms is available on the Internet at http://www.fda.gov.

V. RISKMAP EVALUATION: ASSESSING THE EFFECTIVENESS OF TOOLS AND THE PLAN

As FDA and sponsors seek additional knowledge about the design, effectiveness, burdens, and potential unintended consequences of RiskMAPs, it is important to collect as much information as possible on plan performance. Timely evaluation monitors the effectiveness of RiskMAPs and their component objectives and tools to identify areas for improvement.

A. Rationale for RiskMAP Evaluation

At least two studies have documented poor or limited implementation and effectiveness of traditional risk minimization tools. In particular, the studies examined situations in which labeling changes (with or without Dear Health Care Practitioner letters) were used to reduce safety problems.[9] The iterative process of risk assessment, risk minimization, and reevaluation previously described is intended to avoid repeating these experiences by identifying poorly performing or ineffective RiskMAPs or RiskMAP components as soon as possible. Ultimately, RiskMAP evaluation is intended to ensure that the energy and resources expended on risk minimization are actually achieving the desired goals of continued benefits with minimized risks. FDA considers evaluation of the effectiveness of a RiskMAP to be important and recommends

[9] Smalley W, D Shatin, D Wysowski, J Gurwitz, S Andrade et al., 2000, *Contraindicated Use of Cisapride: Impact of Food and Drug Administration Regulatory Action*. JAMA 284(23):3036-3039; Weatherby LB, BL Nordstrom, D Fife, and AM Walker, 2002, *The Impact Of Wording in "Dear Doctor" Letters and In Black Box Labels*. Clin Pharmacol Ther 72:735-742.

that every RiskMAP contain a plan for periodically evaluating its effectiveness after implementation (see section VII. for a detailed discussion of RiskMAPs).[10]

The evaluation of RiskMAPs can take several forms. Most critical is determining the performance of the overall RiskMAP in achieving its targeted health outcomes or goals. Separate but related assessments can be done for (1) individual tool performance, (2) acceptability of RiskMAP tools by consumers and health care practitioners, and (3) compliance with important RiskMAP processes or procedures.

Generally, FDA anticipates that RiskMAP evaluations would involve the analysis of observational or descriptive data. Statistical hypothesis testing in the context of RiskMAP evaluation would not typically be expected, given the limitations of the data likely to be available.

B. Considerations in Designing a RiskMAP Evaluation Plan

FDA recommends that RiskMAP evaluation plans be tailored to the specific product and designed to assess whether the RiskMAP's goals have been achieved through its objectives and tools. The following are generally applicable guidelines for sponsors designing RiskMAP evaluation plans.

1. Selecting Evidence-Based Performance Measures

The Agency recommends that sponsors select well-defined, evidence-based, and objective performance measures tailored to the particular RiskMAP to determine whether the RiskMAP's goals or objectives are being achieved. An appropriate measure could be a number, percentage, or rate of an outcome, event, process, knowledge, or behavior. Ideally, the chosen measure would directly measure the RiskMAP's health outcome goal. For example, for a RiskMAP with a goal of preventing a particular complication of product use, a sample outcome measure could be to have no more than a specified number or rate of that complication. However, in some cases, a health outcome cannot be practically or accurately measured. In those cases, other measures can be used that are closely related to the health outcome, such as the following:

- surrogates for health outcome measures (e.g., emergency room visits for an adverse consequence, pregnancy tests for pregnancy status)

- process measures that reflect desirable safety behaviors (e.g., performance of recommended laboratory monitoring, signatures attesting to knowledge or discussions of risk)

---

[10] As noted above, sponsors should not develop a RiskMAP for a product for which routine risk minimization measures are sufficient. Similarly, formal evaluation plans and performance measures should not be developed for these products. Instead, evaluation by routine postmarketing surveillance should be sufficient, although some products may also have a Pharmacovigilance Plan as described in the *Pharmacovigilance Guidance*. If a RiskMAP is later developed for this type of product based on new risk information, then a formal evaluation plan may be submitted.

- assessments of comprehension, knowledge, attitudes, and/or desired safety behaviors about drug safety risks (e.g., provider, pharmacist, or patient surveys)

FDA recommends that the validity of a measure be judged by how closely it is related to the desired health outcome goal of the RiskMAP. Simply stated, the more closely related a measure to the RiskMAP goal, the greater its degree of validity. For example, if the RiskMAP goal is avoidance of fetal exposures, then complete ascertainment of pregnancies in the user population would be a highly valid performance measure. The frequency of contraceptive counseling in users could be used, but it is less directly linked to the desired outcome and would be of lower validity as a measure of successful prevention of pregnancy exposures.

2. Compensating for an Evaluation Method's Limitations

Most evaluation measures have limitations. FDA suggests that, in choosing among evaluation methods and measures, sponsors consider their strengths and limitations. The following are examples of some of the limitations of evaluation methods:

- Spontaneous adverse event data are a potentially biased outcome measure because reporting of adverse events varies due to many factors and represents an unknown and variable fraction of the adverse outcomes that are actually occurring. As a result, systematic data collection in defined populations would be recommended for purposes of evaluation.

- Population-based evaluation methods can use administrative or claims-based data systems that capture service or payment claims to measure rates of events, although it is usually recommended that medical records be examined to validate the actual occurrence of coded diagnoses and procedures. Administrative data come from various insurers, purchasing groups, or networks that are often tied to employment, which may mean that individuals at higher risk are excluded because of poor health, advanced age, institutional status, or low socioeconomic status. Also, unless enrollment in an administrative claims system is large, the number of patients exposed to any single product is likely to be limited, as will be the power to detect uncommon adverse events.[11]

- Active surveillance using sentinel reporting sites may be useful for evaluating adverse events, but it is costly and may not detect rare events. Surveys of health care practitioners or patients using various modes (in-person, mail, telephone, electronic) can be another useful form of active surveillance of knowledge, attitudes, policies, and practices of health care practitioners, institutions, and patients about recommended RiskMAP tools and their associated processes. However, issues relating to response rates, representativeness, and reporting biases may limit the accuracy of survey results.[12]

[11] For further discussion of administrative claims systems, please consult the pharmacovigilance guidance.

[12] For a more detailed discussion of survey development and implementation, please consult the pharmacovigilance guidance.

These examples demonstrate how using only one method could skew assessment of the performance of a RiskMAP. Therefore, FDA recommends that, whenever feasible, sponsors design evaluation plans to include at least two different quantitative, representative, and minimally biased evaluation methods for each critical RiskMAP goal. By using two methods, one method can compensate for the limitations of the other. For example, hospitalization data on an adverse event do not capture deaths that occurred out of the hospital; however, coupling such data with death certificate surveillance would offer complementary and more complete ascertainment of mortality risks. If it is not practical to use two complementary and representative methods, FDA suggests using other quantitative methods such as multiple site sampling or audits that aim for high coverage or response rates by the affected population.

3. Evaluating the Effectiveness of Tools in Addition to RiskMAP Goals

FDA recommends that sponsors periodically evaluate each RiskMAP tool to ensure it is materially contributing to the achievement of RiskMAP objectives or goals. Tools that do not perform well may compromise attainment of RiskMAP goals, add unnecessary costs or burdens, or limit access to product benefits without minimizing risks. Tools that are implemented incompletely or in a substandard fashion could result in additional tools being adopted unnecessarily. For all these reasons, evaluating tools is important. Data from such evaluations may make it possible to improve a tool's effectiveness or eliminate the use of a tool that fails to contribute to achieving a RiskMAP goal. By eliminating ineffective tools, resources can be concentrated on useful tools.

Distinguishing between the evaluation of RiskMAP goals and tools is important because the performance of goals and tools may not be linked. For example, the overall goal of a RiskMAP may be achieved despite individual tools performing poorly. The reverse situation may also occur, with component tools performing well but without appropriate progress in achieving the RiskMAP goal. This situation may occur if a surrogate objective correlates poorly to the desired health outcome. The first example (i.e., the RiskMAP goal may be achieved despite individual tools performing poorly) may afford an opportunity to discontinue a tool, whereas its converse may trigger the implementation of new or improved tools, or even a redesign of the overall RiskMAP.

4. Evaluating RiskMAP Tools Prior to Implementation

FDA recommends that, to the extent possible, sponsors evaluate tools before implementation. As discussed in section IV.D. above, FDA suggests that in selecting tools to include in a RiskMAP, a sponsor consider whether the tool will be effective. For example, the success of potential RiskMAP tools might be predicted to some extent by evidence in the scientific literature or from their use in other RiskMAPs.

In addition to considering literature evidence and past RiskMAP experience, FDA recommends that sponsors test a tool before implementation. Pretesting (or pilot testing) can help to assess comprehension, acceptance, feasibility, and other factors influencing how readily RiskMAP tools will fit into patient lifestyles and the everyday practices of health care practitioners. Pretesting can potentially avoid wasted time, expense, and escalation of RiskMAP tools by discriminating

between high- and low-performing tools. For example, if a risk is identified in Phase 1 or 2 trials, Phase 3 trials could provide an opportunity to pretest targeted education and outreach tools.

FDA recommends that pretesting methods be chosen on a case-by-case basis, depending on the product, tool, objective, and goal. For example, in certain preapproval situations, large simple safety studies may be a means of generating useful information about the effectiveness of RiskMAP tools in conditions close to actual practice.[13] On the other hand, for certain tools such as targeted education and outreach, published *best practices* could be used as guidelines for implementation. If time is particularly limited, multiple interviews or focus group testing can assist in determining acceptance or comprehension of a RiskMAP tool by major stakeholder groups. This action might be particularly useful in situations where risks and benefits are closely matched, and RiskMAP goals may include the making of informed therapeutic choices by patients and prescribers.

FDA recognizes that, in some cases, tools cannot be pretested for logistical reasons. Pretesting of tools may not be practical in situations in which newly recognized adverse events dictate the importance of rapid implementation of a RiskMAP after approval and marketing.

C. FDA Assessment of RiskMAP Evaluation Results

FDA recommends that, if a sponsor makes a RiskMAP submission to the Agency, the submission describe when the sponsor will send periodic evaluation results to FDA. As discussed in section VII.B., the Agency recommends that sponsors analyze evaluation results and requests that sponsors provide FDA with (1) the data, (2) all analyses, (3) conclusions regarding effectiveness, and (4) any proposed modifications to the RiskMAP. FDA, in turn, generally would perform its own assessment of RiskMAP effectiveness according to the principles of this guidance.

D. Making Information From RiskMAP Evaluations Available to the Public

As discussed in section IV.C. above, FDA plans to maintain a RiskMAP Web site, including a listing of RiskMAP tools. FDA intends to make available, on the same Web site, general information FDA receives from sponsors and elsewhere about the effectiveness of particular RiskMAP tools in achieving risk minimization objectives. The summaries will not contain information from which a particular sponsor or product could be identified. FDA believes this approach to disclosing information from specific RiskMAP evaluations appropriately balances (1) the Agency's interest in disclosing information to assist sponsors in designing new RiskMAPs and selecting tools with the sponsor's interest in confidentiality, and (2) the Agency's interest in avoiding any disclosure that would create disincentives to adopt RiskMAPs or to conduct or submit to FDA results of RiskMAP evaluations.

[13] For a detailed discussion of large simple safety studies, please consult the premarketing guidance.

VI. COMMUNICATING WITH FDA REGARDING RISKMAP DEVELOPMENT AND DESIGN ISSUES

As discussed above, because risk and benefit information emerge continually throughout a product's lifecycle, a sponsor could decide that a RiskMAP is warranted at several different times. These times include:

- before approval, when a risk is identified from clinical studies, and risk minimization is appropriate as the product is introduced into the marketplace
- after marketing, if pharmacovigilance efforts identify a new serious risk, and minimization of the risk will contribute to a favorable benefit-risk balance
- when marketing a generic product that references an innovator drug with a RiskMAP

If a sponsor would like to initiate a dialogue with FDA to benefit from the Agency's experience in reviewing previously implemented plans, the Agency recommends that the sponsor contact the product's review division. The division may choose to establish a working group to assist the sponsor in developing a RiskMAP. This group could also include representatives from CDER's Office of Drug Safety (ODS), CBER's Office of Biostatics and Epidemiology (Division of Epidemiology), or CDER's Office of Generic Drugs (OGD), as appropriate. In any particular case, it may be helpful if the sponsor and FDA:

- share information and analyses regarding the product's risks and benefits
- discuss the choice of RiskMAP goals, objectives, and tools
- discuss the evaluation plan, including (1) times for evaluation, (2) performance measures, and (3) analyses

Sponsors may wish to discuss RiskMAP issues with FDA at pre-defined meeting times (e.g., end-of-phase-2 meetings), if appropriate, or request meetings where RiskMAPs can be specifically considered. To maximize the value of their discussions with FDA, we recommend that sponsors who seek the Agency's guidance apprise reviewers of the rationale for and data underlying RiskMAPs under consideration. FDA requests that sponsors also share relevant background information and questions for discussion before their meetings with FDA.

If the sponsor decides to submit a RiskMAP before marketing approval of the product, FDA recommends that the RiskMAP be submitted to the investigational new drug application (IND), new drug application (NDA), or biologics license application (BLA) for the product in question. If a RiskMAP is being considered in a product's postmarket phase, FDA recommends that it be submitted as a supplement to the relevant NDA or BLA.

FDA encourages early and open discussion of safety concerns and whether such concerns may merit a RiskMAP. Early discussion of RiskMAPs could provide the opportunity to pretest risk minimization tools.

675
676
677 **VII. RECOMMENDED ELEMENTS OF A RISKMAP SUBMISSION TO FDA**
678
679 **A. Contents of a RiskMAP Submission to FDA**
680
681 FDA suggests that a RiskMAP submission to FDA include the following sections, as well as a
682 table of contents:
683
684 • Background
685 • Goals and Objectives
686 • Strategy and Tools
687 • Evaluation Plan
688
689 *1. Background*
690
691 FDA suggests that the Background section explain why a RiskMAP is being considered and
692 created. We recommend that it describe the risks to be minimized and the benefits that would be
693 preserved by implementation of a RiskMAP. Further, we suggest that this section describe, to
694 the extent possible, the type, severity, frequency, and duration of the product's risks, with
695 particular attention to the risk or risks addressed by the RiskMAP.
696
697 The following are sample questions regarding risk characterization that we recommend be
698 addressed in the Background section:
699
700 • What is the rationale for the RiskMAP?
701 • What is the risk the RiskMAP addresses? Is there more than one risk to be minimized?
702 If there is, how do they relate to each other with regard to the following bulleted items?
703 • What is the magnitude and severity of the risk?
704 • Who is at highest risk?
705 • Are particular populations at risk (e.g., children, pregnant women, the elderly)?
706 • Is the risk predictable?
707 • Is the risk preventable?
708 • Is the risk reversible?
709 • Is the risk time-limited, continuous, or cumulative?
710
711 FDA recommends that this section include a discussion that considers the product's risks in the
712 context of its benefits. The following are sample questions that address benefit characterization.
713
714 • What is the overall nature or extent of benefit and what are the expected benefits over
715 time (i.e., long-term benefits)?
716
717 • How do the populations most likely to benefit from this product compare to those that
718 may be at highest risk?
719

- How would implementation of a RiskMAP affect individual and population benefits? Will it increase the likelihood that benefits will exceed risks in patients using the product? Will the RiskMAP preserve access to the product by patients who benefit from it?

- Could certain individuals and/or populations likely to benefit from the product potentially have less access to the product because of the tools in the RiskMAP?

We suggest that the Background section include a discussion, if pertinent, about the successes and failures of other regulatory authorities, systems of health care, or sponsor actions in minimizing the risks of concern. Information provided by the sponsor regarding relevant past experiences, domestically or in other countries, will assist in harmonizing plans as well as avoiding the cost of implementing RiskMAP tools already deemed unsuccessful.

2. Goals and Objectives

FDA suggests that the Goals and Objectives section describe the goals and objectives of the RiskMAP.[14] In addition, we recommend that this section describe how the stated objectives will individually and collectively contribute to achieving the goal or goals.

3. *Strategy and Tools*

FDA suggests that the Strategy and Tools section define the overall strategy and tools to be used to minimize the risk or risks targeted by the RiskMAP. We recommend that the sponsor provide a rationale for choosing the overall strategy. We suggest that the sponsor describe how each tool fits into the overall RiskMAP and its relationship to the other tools. FDA suggests that the sponsor also provide the rationale for choosing each tool (see section IV.D. for a discussion of considerations in choosing tools). In particular, we recommend that the sponsor describe the available evidence regarding the tool's effectiveness and, where applicable, provide results from pretesting. In addition, we suggest that the sponsor state whether it sought input from key groups, and if it did, we suggest that the sponsor describe the feedback that was received regarding the feasibility of its RiskMAP.

We recommend this section also include an implementation scheme that describes how and when each RiskMAP tool would be implemented and coordinated. FDA suggests that sponsors specify overall timelines and milestones. For example, this section could address whether targeted education and outreach tools would be implemented before, or concurrently with, other tools.

4. Evaluation Plan

FDA suggests that the Evaluation Plan section describe the evaluation measurements or measures that will be used to periodically assess the effectiveness of the RiskMAP's goals, objectives, and tools. For a detailed discussion of RiskMAP evaluation, see section V.

[14] See section IV for a discussion of goals and objectives.

We recommend that this section include:

- The proposed evaluation methods for assessing RiskMAP effectiveness (e.g., claims-based data systems, surveys, registries) and the rationales for the sponsor's chosen measures.

- Targeted values for each measure and the time frame for achieving them. FDA recommends the sponsor include interpretations of expected results under best- and worst-case scenarios. In addition, we suggest the sponsor specify what values of measures at specific time points will trigger consideration of RiskMAP modification.

- The nature and timing of data collection, analyses, and audits or monitoring that will be used to assess the performance of each individual tool in achieving the RiskMAP's objectives and goals. Again, we suggest specifying target values for measures.

- A schedule for submitting progress reports to FDA regarding the evaluation results for the RiskMAP's individual tools, objectives, and goals (see section VII.B. for a discussion of progress reports). We recommend that the timing and frequency of progress reports be based primarily on the nature of the risk, tools used, and outcomes under consideration. FDA recommends that progress reports be included in periodic safety update reports or traditional periodic reports.

Where applicable and possible, we recommend that the Evaluation Plan section discuss potential unintended and untoward consequences of the RiskMAP. Such a discussion would be particularly valuable if there are therapeutic alternatives with similar benefits and risks. We suggest that sponsors discuss how unintended consequences would be assessed after RiskMAP implementation. The goal of the assessment would be to ensure that overall population risks are minimized and specific product benefits, including access, are preserved.

B. Contents of a RiskMAP Progress Report

FDA recommends that a RiskMAP progress report contain the following sections, accompanied by a table of contents:

- Summary of the RiskMAP
- Methodology
- Data
- Results
- Discussion and Conclusions

1. Summary

We suggest that the Summary section briefly provide background on and an overview of the RiskMAP, and describe the overall RiskMAP goals and objectives, as well as its strategy and tools. We recommend that this section also summarize (1) the evaluation methods used and (2) the relevant measures and time frames for achieving targeted values.

2. Methodology

We recommend that the Methodology section provide a brief overview of the evaluation methods used (e.g., comprehension testing, patient surveys, process audits). FDA suggests that it describe the evaluation plan, sources of potential measurement error or bias, and the analytical methods used to account for them. Since RiskMAP evaluations will often rely upon observational data, we recommend that the analytical plan address issues such as measurement errors, sensitivity, and specificity of the measures, as well as power and confidence intervals where appropriate.

3. Data

To the extent possible, we recommend that the Data section of a RiskMAP progress report contain the primary data from each evaluation method.

4. Results

FDA suggests that the Results section contain analyses of the evaluation data, statistical estimation, and the sponsor's comparison of tool, objective, and/or goal performance relative to targeted measures.

5. Discussion and Conclusions

FDA recommends that this section describe whether the RiskMAP is meeting or has met the stated measures for each tool, objective, and goal. We suggest that this discussion take all available data, evaluations, and analyses into consideration.

In some cases, the sponsor may choose to propose modifications to the RiskMAP if the RiskMAP goals were not achieved.