

RISK MANAGEMENT

FDA Guidance for Industry

- Premarketing Risk Assessment
- Development and Use of Risk Minimization Action Plans (RiskMAPs)
- Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment

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Minimization Action Plans (RiskMAPs)

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Pharmacoepidemiologic Assessment



United BioSource Corporation

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New Risk Management initiatives represent some of the most important events affecting drug safety to appear in decades. These initiatives will have tremendous impact on drug development and regulation. Not surprisingly, then, Risk Management is on everyone's mind today. We are all continually seeking new and better ways to evaluate the risks and benefits of our pharmaceutical and biotechnology products and medical devices, and to create risk management interventions when needed to protect the public health.

This series of three FDA Guidance Documents, issued in March 2005, sets the framework for thinking about Risk Management as a continuum during the drug development and commercialization processes. Pre-Marketing Risk Assessment emphasizes the importance of establishing a robust clinical trial safety database during development and of thoroughly understanding disease natural history. This guidance, focused on phase III of drug development, points out that more data are needed on patient subgroups, longer duration effects and infrequent events. Importantly, this guidance notes the important role of large simple safety studies in phases III and IV. The Guidance on Development and Use of Risk Minimization Action Plans (Risk MAPs) outlines the context for creating a Risk MAP with considerations for the elements of the plan, the selection of appropriate risk intervention tools, and the importance of an evaluation strategy. The third Guidance, Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment, provides advice on spontaneous adverse event data collection and identification of safety signals. Additionally it gives guidance on using pharmacoepidemiologic methods such as registries, surveys, and database studies for signal evaluation.

We at UBC are committed to working with you in all aspects of risk assessment, risk intervention, and risk management evaluation. UBC delivers evidence-based services to enhance the medical and commercial potential of pharmaceuticals, biologics, medical devices and diagnostics. Our years of experience in strategic consulting, safety surveillance, and regulatory-mandated programs give us the ability to work with you to address risk management issues. We are prepared to assist in developing pharmacovigilance plans, designing and conducting large streamlined trials and registries, and creating risk minimization plans and interventions.

We trust that you will find this compendium of FDA Risk Management Guidances a useful reference to help integrate these new approaches into your drug development and launch activities.

Sincerely,



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RISK MANAGEMENT

FDA Guidance for Industry

Premarketing Risk Assessment

PREMARKETING RISK ASSESSMENT

This guidance represents 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 good risk assessment practices during the development of prescription drug products, including biological drug products.[2] This is one of three guidances that were developed to address risk management activities. Specifically, this document discusses the generation, acquisition, analysis, and presentation of premarketing safety data.

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

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 developing three draft guidance documents on risk management activities.

The draft guidance documents were published on May 5, 2004, and the public was provided with an opportunity to comment on them until July 6, 2004. FDA considered all of the comments received in producing the final guidance documents.

- Premarketing Risk Assessment (Premarketing Guidance)
- Development and Use of Risk Minimization Action Plans (RiskMAP Guidance)
- Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment (Pharmacovigilance Guidance).

B. Overview of the Risk Management Guidances

Like the concept papers and draft guidances that preceded them, each of the three final 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 (see e.g., FDA requirements for professional labeling and adverse event monitoring and reporting). As a result, many

of the recommendations presented here focus on situations in which a product may pose a clinically important and unusual type or level of risk. To the extent possible, we have specified in the text whether a recommendation is intended for 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]

- To the extent possible, this guidance reflects FDA's commitment to harmonization of international definitions and standards.
- When planning risk assessment and risk minimization activities, sponsors should consider input from healthcare participants likely to be affected by these activities (e.g., from consumers, pharmacists and pharmacies, physicians, nurses, and 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 ASSESSMENT IN RISK MANAGEMENT

Risk management is an iterative process designed to optimize the benefit-risk balance for regulated products. Risk assessment consists of identifying and characterizing the nature, frequency, and severity of the risks associated with the use of a product. Risk assessment occurs throughout a product's lifecycle, from the early identification of a potential product, through the premarketing development process, and after approval during marketing. Premarketing risk assessment represents the first step in this process, and this guidance focuses on risk assessment prior to marketing.

It is critical to FDA's decision on product approval that a product's underlying risks and benefits be adequately assessed during the premarketing period. Sponsors seeking approval must provide from the clinical trials a body of evidence that adequately characterizes the product's safety profile.[4]

This guidance provides general recommendations for assessing risk. The adequacy of the assessment of risk is a matter of both quantity (ensuring that enough patients are studied) and quality (the appropriateness of the assessments performed, the appropriateness and breadth of the patient populations studied, and how results are analyzed). Quantity is, in part, considered in other Agency guidances,[5] but it is discussed further here. This guidance also addresses the qualitative aspects of risk assessment.

Although risk assessment continues through all stages of product development, this guidance focuses on risk assessment during the later stages

of clinical development, particularly during phase 3 studies. The guidance is not intended to cover basic aspects of preclinical safety assessments (i.e., animal toxicity testing) or routine clinical pharmacology programs. Good clinical risk assessment in the later stages of drug development should be guided by the results of comprehensive preclinical safety assessments and a rigorous, thoughtful clinical pharmacology program (including elucidation of metabolic pathways, identification of possible drug-drug interactions, and determination of any effects from hepatic and/or renal impairment). These issues are addressed in other FDA guidances and guidances developed under the auspices of the International Conference for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH).

IV. GENERATING RISK INFORMATION DURING CLINICAL TRIALS

Providing detailed guidance on what constitutes an adequate safety database for all products is impossible. The nature and extent of safety data that would provide sufficient information about risk for purposes of approving a product are individualized decisions based on a number of factors (several of which are discussed below). In reaching a final decision on approvability, both existing risk information and any outstanding questions regarding safety are considered in a product's risk assessment and weighed against the product's demonstrated benefits. The fewer a product's demonstrated benefits, the less acceptable may be higher levels of demonstrated risks. Likewise, the fewer the benefits, generally, the less uncertainty may be accepted about a product's risks.

To maximize the information gained from clinical trials, FDA recommends that from the outset of development, sponsors pay careful attention to the overall design of the safety evaluation. Potential problems that may be suspected because of preclinical data or because of effects of related drugs should be targeted for evaluation. And, because it is impossible to predict every important risk, as experience accrues, sponsors should refine or modify their safety evaluations.

A. Size of the Premarketing Safety Database

Even large clinical development programs cannot reasonably be expected to identify all risks associated with a product. Therefore, it is expected that, even for a product that is rigorously tested preapproval, some risks will become apparent only after approval, when the product is used in tens of thousands or even millions of patients in the general population. Although no preapproval database can possibly be sized to detect all safety issues that might occur with the product once marketed in the full population, the larger and more comprehensive the preapproval database, the more likely it is that serious adverse events will be detected during drug development.

The appropriate size of a safety database supporting a new product will depend on a number of factors specific to that product, including:

- Its novelty (i.e., whether it represents a new treatment or is similar to available treatment)
- The availability of alternative therapies and the relative safety of those alternatives as compared to the new product

- The intended population and condition being treated
- The intended duration of use

Safety databases for products intended to treat life-threatening diseases, especially in circumstances where there are no alternative satisfactory treatments, are usually smaller than for products intended to treat diseases that are neither life-threatening nor associated with major, irreversible morbidity. A larger safety database may be appropriate if a product's preclinical assessment or human clinical pharmacology studies identify signals of risk that warrant additional clinical data to properly define the risk. The appropriate size of the preapproval safety database may warrant specific discussion with the relevant review division. For instance, 21 CFR 312.82(b) (subpart E) provides that for drugs intended to treat life-threatening and seriously debilitating illnesses, end-of-phase 1 meetings can be used to agree on the design of phase 2 trials "with the goal that such testing will be adequate to provide sufficient data on the drug's safety and effectiveness to support a decision on its approvability for marketing."

For products intended for short-term or acute use (e.g., treatments that continue for, or are cumulatively administered for, less than 6 months), FDA believes it is difficult to offer general guidance on the appropriate target size of clinical safety databases. This is because of the wide range of indications and diseases (e.g., acute strokes to mild headaches) that may be targeted by such therapies. Sponsors are therefore encouraged to discuss with the relevant review division the appropriate size of the safety database for such products. Because products intended for life-threatening and se-

verely debilitating diseases are often approved with relatively small safety databases, relatively greater uncertainty remains regarding their adverse effects. Similarly, when products offer a unique, clinically important benefit to a population or patient group, less certainty in characterizing risk prior to approval may be acceptable.

For products intended for long-term treatment of non-life-threatening conditions, (e.g., continuous treatment for 6 months or more or recurrent intermittent treatment where cumulative treatment equals or exceeds 6 months), the ICH and FDA have generally recommended that 1500 subjects be exposed to the investigational product (with 300 to 600 exposed for 6 months, and 100 exposed for 1 year).[6] For those products characterized as chronic use products in the ICH guidance E1A, FDA recommends that the 1500 subjects include only those who have been exposed to the product in multiple dose studies, because many adverse events of concern (e.g., hepatotoxicity, hematologic events) do not appear with single doses or very short-term exposure. Also, the 300 to 600 subjects exposed for 6 months and 100 subjects exposed for 1 year should have been exposed to relevant doses (i.e., doses generally in the therapeutic range)

We note that it is common for well-conducted clinical development programs to explore doses higher than those ultimately proposed for marketing. For example, a dose tested in clinical trials may offer no efficacy advantage and show some dose-related toxicities; therefore, the sponsor does not propose the dose for marketing when the application is submitted. In such cases, data from subjects exposed to doses in excess of those ultimately proposed are highly informative for the safety evaluation and should be counted as contributing to the relevant safety database.

The E1A guidance describes a number of circumstances in which a safety database larger than 1500 patients may be appropriate, including the following:

1. There is concern that the drug would cause late developing adverse events, or cause adverse events that increase in severity or frequency over time. The concern could arise from:
 - Data from animal studies
 - Clinical information from other agents with related chemical structures or from a related pharmacologic class
 - Pharmacokinetic or pharmacodynamic properties known to be associated with such adverse events
2. There is a need to quantitate the occurrence rate of an expected specific low-frequency adverse event. Examples would include situations where a specific serious adverse event has been identified in similar products or where a serious event that could represent an alert event is observed in early clinical trials.
3. A larger database would help make risk-benefit decisions in situations when the benefit from the product:
 - Is small (e.g., symptomatic improvement in less serious medical conditions)
 - Will be experienced by only a fraction of the treated patients (e.g., certain preventive therapies administered to healthy populations)

— Is of uncertain magnitude (e.g., efficacy determination on a surrogate endpoint)

4. Concern exists that a product may add to an already significant background rate of morbidity or mortality, and clinical trials should be designed with a sufficient number of patients to provide adequate statistical power to detect prespecified increases over the baseline morbidity or mortality.

The determination of whether the above provisions of the ICH E1A guidance are appropriate for a particular product development program and how these considerations would best be addressed by that program calls for evaluation on a case-by-case basis. Therefore, FDA recommends that this issue be discussed with the relevant review division at the end-of-phase 2 meeting, if not earlier.

In addition to the considerations provided in E1A, there are other circumstances in which a larger database may be appropriate.

1. The proposed treatment is for a healthy population (e.g., the product under development is for chemoprevention or is a preventive vaccine).
2. An effective alternative to the investigational product is already available and has been shown to be safe.

FDA is not suggesting that development of a database larger than that described in E1A is required or should be the norm. Rather, the appropriate database size would depend on the circumstances affecting a particular product, including the considerations outlined above. Therefore, FDA recommends that sponsors communicate with the review

division responsible for their product early in the development program (e.g., at the pre-IND meeting) on the appropriate size of the safety database. FDA also recommends that sponsors revisit the issue at appropriate regulatory milestones (e.g., end-of-phase 2 and pre-NDA meetings).

B. Considerations for Developing a Premarketing Safety Database

Although the characteristics of an appropriate safety database are product-specific, some general principles can be applied. In general, efforts to ensure the quality and completeness of a safety database should be comparable to those made to support efficacy. Because data from multiple trials are often examined when assessing safety, it is particularly critical to examine terminology, assessment methods, and use of standard terms (e.g., use of the Medical Dictionary for Regulatory Activities (MedDRA)) to be sure that information is not obscured or distorted. Ascertainment and evaluation of the reasons for leaving assigned therapy during study (deaths and dropouts for any reason) are particularly important for a full understanding of a product's safety profile.

The following elements should be considered by sponsors when developing proposals for their clinical programs as these programs pertain to risk assessment.

1. Long-Term Controlled Safety Studies

It is common in many clinical programs for much of subject exposure data and almost all of long-term exposure data to come from single-arm or uncontrolled studies. Although these data can be informative, it may be preferable in some circumstances

to develop controlled, long-term safety data. Such data allow for comparisons of event rates and facilitate accurate attribution of adverse events. Control groups may be given an active comparator or a placebo, depending on the disease being treated (i.e., the ethical and medical feasibility of using a placebo versus an active comparator will depend on the disease being treated).

The usefulness of active comparators in long-term safety studies depends on the adverse events of interest.

- Generally, serious events that rarely occur spontaneously (e.g., severe hepatocellular injury or aplastic anemia) would be considered significant and interpretable whenever (1) they are clearly documented and (2) there is no likely alternative explanation, since the expected rate is essentially zero in populations of any feasible size. As a result, the events can usually be appropriately interpreted and regarded as a signal of concern whether or not there is a control group.
- On the other hand, control groups are needed to detect increases in rates of events that are relatively common in the treated population (e.g., sudden death in patients with ischemic cardiac disease). Control groups are particularly important when an adverse event could be considered part of the disease being treated (e.g., asthma exacerbations occurring with inhalation treatments for asthma).

Therefore, FDA decisions as to when long-term comparative safety studies should be conducted

for a product should be based on the intended use of the product, the nature of the labeled patient population (e.g., more useful if there is a high rate of serious adverse events), and earlier clinical and preclinical safety assessments. Although it is clear that long-term controlled studies will not usually be conducted, such studies may be particularly useful when a safety issue is identified during earlier development of the drug. In these cases, safety studies designed to test specific safety hypotheses may be appropriate. This would be especially true in situations where the safety issue of concern is more common with cumulative exposure. (See section IV.D below for further discussion of comparative trials.)

2. A Diverse Safety Database

Premarketing safety databases should include, to the extent possible, a population sufficiently diverse to adequately represent the expected target population, particularly in phase 3 studies. FDA has previously addressed this issue in a memorandum,^[7] and the recommendations provided here are intended to supplement that document. To the extent feasible, only patients with obvious contraindications or other clinical considerations that clearly dictate exclusion should be excluded from study entry. Inclusion of a diverse population allows for the development of safety data in a broad population that includes patients sometimes excluded from clinical trials, such as the elderly (particularly the very old), patients with concomitant diseases, and patients taking concomitant medications. Broadening inclusion criteria in phase 3 enhances the generalizability of the safety (and efficacy) findings. Although some phase 3 efficacy studies may target certain demographic or disease characteristics (and have narrower inclusion and exclusion

criteria), overall, the phase 3 studies should include a substantial amount of data from less restricted populations.

3. Exploring Dose Effects Throughout the Clinical Program

Currently, it is common for only one dose, or perhaps a few doses, to be studied during drug development beyond phase 2. Yet, a number of characteristics common to many phase 2 studies limit the ability of these trials to provide definitive data on exposure-response or adequate data for definitive phase 3 dose selection. These characteristics of phase 2 studies (in comparison to phase 3 studies) include the following:

- Shorter durations of exposure
- Common use of pharmacodynamic (PD) endpoints, rather than clinical outcomes
- Smaller numbers of patients exposed
- Narrowly restrictive entry criteria

Although phase 3 trials do not necessarily need to examine a range of doses, such an examination is highly desirable, particularly when phase 2 studies cannot reasonably be considered to have established a single most appropriate dose. When a dose is not established in phase 2, more than one dose level should be examined in phase 3 trials of fixed dose products to better characterize the relationship between product exposure and resulting clinical benefit and risk. Dose-response data from phase 3 trials with multiple dose levels will help to better define the relationship of clinical response to dose for both safety and effectiveness. Furthermore, inad-

equate exploration of a product's dose-response relationship in clinical trials can raise safety concerns, since recommending doses in labeling that exceed the amount needed for effectiveness may increase risk to patients through dose-related toxicities with no potential for gain. Exposure-response data from phase 3 trials can also provide critical information on whether dose adjustments should be made for special populations. Finally, demonstrating a dose-response relationship in late phase clinical trials with meaningful clinical endpoints may aid the assessment of efficacy, since showing a dose ordering to efficacy can be compelling evidence of effectiveness.[8] When multiple dose levels are examined in phase 3 trials, the appropriate choice of doses to be included in these studies would be based on prior efficacy and safety information, including prior dose-ranging studies. In these circumstances, an end-of-phase 2 meeting with the appropriate review division would be particularly useful.

C. Detecting Unanticipated Interactions as Part of a Safety Assessment

Even a well-conducted and reasonably complete general clinical pharmacology program does not guarantee a full understanding of all possible risks related to product interactions. Therefore, risk assessment programs should examine a number of interactions during controlled safety and effectiveness trials and, where appropriate, in specific, targeted safety trials. This examination for unanticipated interactions should include the potential for the following:

- Drug-drug interactions in addition to those resulting from known metabolic pathways (e.g., the effect of azole antibiotics on a CYP 3A4 dependent drug)

We recommend that these examinations target a limited number of specific drugs, such as likely concomitant medications (e.g., for a new cholesterol lowering treatment, examining the consequences of concomitant use of HMG CoA reductase inhibitors and/or binding resins). The interactions of interest could be based, for example, on known or expected patterns of use, indications sought, or populations that are likely users of the drug.

- Product-demographic relationships — by ensuring sufficient diversity of the population (including gender, age, and race) to permit some assessments of safety concerns in demographic population subsets of the intended population
- Product-disease interactions — by ensuring sufficient variability in disease state and concomitant diseases
- Product-dietary supplement interactions for commonly used supplements that are likely to be co-administered or for which reasonable concerns exist (e.g., examination of the interactions between a new drug for the treatment of depression and St. John's Wort).

Again, FDA recommends that any such examinations target likely concomitant use based, for example, on indications sought, intended patterns of use, or the population of intended users of the drug and based on a history of drug and dietary supplement use elicited from subjects.

Generally, a sponsor determines its product's intended use and intended population(s) during product development. Decisions as to which interactions to either explore or specifically test in clinical trials

could be based on these determinations and/or surveys and epidemiologic analyses.

One important way to detect unexpected relationships is by systematic incorporation of pharmacokinetic (PK) assessments (e.g., universal steady state sampling or population PK analyses) into some or all of the later phase clinical trials, including any specific safety trials. PK assessments can aid in the detection of unexpected PK interactions and, in some cases, could suggest exposure-response relationships for both safety and efficacy. Such data would allow for better assessment of whether pharmacokinetics contribute to any adverse events seen in the clinical trials, particularly rare, serious, and unanticipated events.

When a product has one or more well-established, valid biomarkers pertinent to a known safety concern, the marker should be studied during the PK studies and clinical development (e.g., creatine phosphokinase assessments used in the evaluation of new HMG CoA reductase inhibitors as a marker for rhabdomyolysis, or assessments of QT/QTc effects for new antihistamines).

D. Developing Comparative Safety Data

Depending on the drug and its indication, much of the safety data in an application may be derived from placebo-controlled trials and single-arm safety studies, with little or no comparative safety data. Although comparative safety data from controlled trials comparing the drug to an active control (these could also include placebo group) generally are not necessary, situations in which such data would be desirable include the following:

— The background rate of adverse events is high.

The new drug may seem to have a high rate of adverse events in a single-arm study when, in fact, the rate is typical of that for other drugs. The additional use of a placebo would help to show whether either drug actually caused the adverse events.

— There is a well-established treatment with an effect on survival or irreversible morbidity.

In such cases, not only are comparative data important scientifically, but the use of the comparator would likely be required ethically, as a placebo control could not be used and a single-arm trial would generally be uninformative.

— The sponsor hopes to claim superiority for safety or effectiveness.

If a comparative effectiveness claim were sought, it would be expected that the studies would also address comparative safety, since a gain in effectiveness could be outweighed by or negated by an accompanying safety disadvantage.

In situations where there is a well-established related therapy, a comparative study of the new agent against that well-established therapy would be desirable (e.g., a new NSAID-like drug could be compared to a market-leading NSAID). Such a study could show whether the toxicity profile for the established therapy is generally similar to that for the novel therapy or whether important differences exist.

V. SPECIAL CONSIDERATIONS FOR RISK ASSESSMENT

Although many of the previous comments and recommendations are intended to apply to new product development programs generally, some risk assessment issues would apply only in certain circumstances or to certain types of products. [9]

A. Risk Assessment During Product Development

The following are examples of how risk assessment strategies could be tailored to suit special situations, where appropriate.

- If a product is intended to be chronically used (particularly when it has a very long half-life) and/or has dose-related toxicities, it can be useful to examine whether a lower or less frequent maintenance dose would be appropriate.
- If a product's proposed dosing includes a proposed titration scheme, the scheme could be based on specific studies to define how titration is best performed and the effects of titration on safety and efficacy.
- Certain kinds of adverse effects are not likely to be detected or readily reported by patients without special attention. When a drug has the potential for such effects, additional testing or specific assessments within existing trials may be appropriate.

For example, for a new drug with recognized CNS effects (especially sedating effects), sponsors should conduct an assessment of cognitive func-

tion, motor skills, and mood. Similarly, since many antidepressants have significant effects on sexual function, new antidepressants should be assessed for these effects. The use of targeted safety questionnaires or specific psychometric or other validated instruments is often important for such assessments, since routine adverse event monitoring and safety assessments tend to underestimate or even entirely miss such effects.

- If a product is to be studied in pediatric patients, special safety issues should be considered (e.g., effects on growth and neurocognitive development if the drug is to be given to very young children/infants; safety of excipients for the very young; universal immunization recommendations and school entry requirements for immunization).
- A sponsor may consider reserving blood samples (or any other bodily fluids/tissues collected during clinical trials) from some or all patients in phase 3 studies for possible assessments at a later time, particularly in circumstances when earlier safety data signal an unusual or important concern. Such later assessments could include pharmacogenomic markers, assessments for immunogenicity, or measurements of other biomarkers that might prove helpful clinically. Having samples available for retrospective analysis of pharmacogenomic markers could help to link the occurrence of serious adverse events to particular genetic markers (e.g., haplotypes).

In unusual circumstances, a large, simple, safety study (LSSS) may be appropriate. An LSSS is usually a randomized clinical study designed to assess

limited, specific outcomes in a large number of patients. These outcomes — generally important safety endpoints or safety concerns suggested by earlier studies — should be defined a priori with the study specifically designed to assess them. Although the large simple study model arose in the context of effectiveness assessment, and thus always involved randomized, controlled trials, an LSSS could in some cases be useful even without a control group — for example, to assess the rate of rare events (i.e., events so uncommon that usual safety studies would not be expected to provide good estimates of risk). Although an LSSS would most commonly be performed postapproval, either as a phase 4 commitment to address a lingering safety issue that does not preclude approval or outside of a formal phase 4 commitment in response to a new safety concern that arises after marketing, there are instances where an LSSS may be appropriate prior to approval. This would be the case when, for instance, there is a significant safety signal of concern (e.g., hepatotoxicity, myotoxicity) arising out of the developing clinical trial database that is not sufficiently resolved by the available data or is unlikely to be sufficiently addressed by the remaining ongoing studies. In these circumstances, an LSSS may be appropriate if the safety signal cannot otherwise be better delineated and the safety signal would have an impact on approvability.[10]

In addition, a sponsor seeking to develop a product for preventive use in at-risk, but otherwise healthy, individuals could conduct a large trial to investigate the product's safety. The use of a large trial may increase the chance of showing the product to have an acceptable benefit-risk profile in such cases, because the potential for benefit in the exposed population would generally be small. Such large trials,

though not always LSSSs in a strict sense, may in some cases appropriately employ limited, targeted evaluations of both efficacy and safety endpoints, similar to an LSSS.

B. Assessing and Minimizing the Potential for Medication Errors

Sponsors can help minimize the occurrence of medication errors by assessing, prior to marketing, common sources of medication errors. Such errors may arise because of the product's inherent properties or because of the inadvertent contribution of the proposed proprietary name, the established name, the proposed labeling (e.g., container, carton, patient/consumer labeling, or professional package insert), and the proposed packaging.

Some medication errors, especially those involving parenteral products, have been detected in clinical trials prior to marketing. When occurring in clinical trials, events such as improper dilution or improper administration techniques, which may result in non-optimal dosing, should be carefully examined as warning signs that the product could be subject to dosing errors that warrant changes in labeling, packaging, or design. Even if errors are not observed in trials, careful consideration should be given during development to the implications of the design of the product, its packaging, and any device used to administer or deliver the product. For example, when a concentrated product that requires further dilution prior to intravenous administration is being developed, packaging is important. Packaging such a product in a syringe would make it possible to inject the product as a bolus without proper dilution, increasing risks to patients. Similarly, when developing a product that is administered or delivered by a device, the implications of me-

chanical failure of the device should be examined. Any such occurrences seen or considered during product development should be documented, reported, and analyzed for potential remedial actions (e.g., redesign of the device or modification of instructions for use).

Medication errors arising from confusion because of the similarity of the drug name, when written and spoken, to the name of another drug are less likely to be detected prior to marketing due to the controlled environment of clinical trials. However, the many well-documented cases of medication errors associated with similar proprietary names, confusing labels and labeling, and product packaging suggest it is important that sponsors carefully consider these issues before marketing a product.

Premarketing assessments should focus on:

- Identifying all medication errors that occur during product development
- Identifying the reasons or causes for each identified error (e.g., dosage form, packaging, labeling, or confusion due to trade names when written or spoken)
- Assessing the resultant risk in the context of how and in whom the product will be used
- Identifying the means to minimize, reduce or eliminate the medication errors by ensuring the proper naming, labeling, design, and packaging of the product

Depending on the nature of the product, the indication, how it is administered, who will be receiving it, and the context in which it will be used, one or

more of the following techniques may be helpful in assessing and preventing medication errors:

- Conducting a Failure Mode and Effects Analysis[11], [12]
- Use of expert panels
- Use of computer-assisted analysis
- Use of direct observation during clinical trials
- Directed interviews of consumers and medical and pharmacy personnel to better understand comprehension
- Use of focus groups
- Use of simulated prescription and over-the-counter (OTC) use studies

Additional information on the application of these assessment techniques will be published in a future guidance document.

C. Addressing Safety Aspects During Product Development

FDA recommends addressing the potential for the following serious adverse effects as a part of the new drug application (NDA) for all new small molecule drugs:

- Drug-related QTc prolongation
- Drug-related liver toxicity
- Drug-related nephrotoxicity

- Drug-related bone marrow toxicity
- Drug-drug interactions
- Polymorphic metabolism

Prior experience has shown that these effects can often be identified when properly assessed in clinical development programs. Although FDA believes it is important to address these potential effects in all NDAs, adequately addressing all of these considerations would not necessarily involve the generation of additional data or the conduct of specific trials. (For some issues, such as QTc, specifically conducted preclinical and clinical studies are generally recommended.) For example, a drug that is intended to be topically applied may be shown to have no systemic bioavailability; therefore, systemic toxicities would be of no practical concern.

Some of the above-listed potential effects are relevant to biological products; some are not. In addition, for biological products such as cytokines, antibodies, other recombinant proteins, and cell-, gene-, and tissue-based therapeutics, it may be appropriate to assess other issues. The issues listed here are dependent on the specific nature of the biological product under development.

- Potentially important issues for biological products include assessments of immunogenicity, both the incidence and consequences of neutralizing antibody formation and the potential for adverse events related to binding antibody formation.
- For gene-based biological products, transfection of nontarget cells and transmissibility of infection to close contacts, and the

genetic stability of products intended for long-persistence transfections constitute important safety issues.

- For cell-based products, assessments of adverse events related to distribution, migration, and growth beyond the initial intended administration are important, as are adverse events related to cell survival and demise. Such events may not appear for a long time after product administration.

A complete discussion of assessment of safety issues unique to biological products is beyond the scope of this guidance. We recommend that sponsors address the unique safety concerns pertaining to the development of any particular biological product with the relevant product office.

VI. DATA ANALYSIS AND PRESENTATION

Many aspects of data analysis and presentation have been previously addressed in guidance, most notably in FDA's Guideline for the Format and Content of the Clinical and Statistical Sections of an Application and the ICH guidances E3 Structure and Content of Clinical Study Reports and M4 Common Technical Document for the Registration of Pharmaceuticals for Human Use. We do not repeat that guidance here, but offer new guidance on selected issues.

With regard to the guidance offered in this section of the document, it is important to emphasize that the regulatory approach to the evaluation of the safety of a product usually differs substantially from the evaluation of effectiveness. Most studies in the later phases of drug or biologic development are directed toward establishing effectiveness. In such

studies, critical efficacy endpoints are identified in advance, and statistical planning is conducted based on being able to make definitive statistical inferences about efficacy. In contrast, these later phase trials are not generally designed to test specified hypotheses about safety or to measure or identify adverse events with any prespecified level of sensitivity. Therefore, the premarket safety evaluation is often, by its nature, exploratory and is intended to identify common adverse events related to the therapy, as well as to help identify signals for serious and/or less common adverse events.

A. Describing Adverse Events to Identify Safety Signals

Because individual investigators may use different terms to describe a particular adverse event, FDA recommends that sponsors ensure that each investigator's verbatim terms are coded to standardized, preferred terms specified in a coding convention or dictionary. Proper coding allows similar events that were reported using different verbatim language to be appropriately grouped. Consistent and accurate coding of adverse events allows large amounts of data regarding these events to be analyzed and summarized and maximizes the likelihood that safety signals will be detected. Inaccurate coding, inconsistent coding of similar verbatim terms, and inappropriate "lumping" of unrelated verbatim terms or "splitting" of related verbatim terms can obscure safety signals.

In general, FDA suggests that sponsors use one coding convention or dictionary (e.g., MedDRA) throughout a clinical program with the understanding that, due to the duration of product development, the coding convention used may undergo revisions. Use of more than one coding convention

or dictionary can result in coding differences that prevent adverse event data from being appropriately grouped and analyzed. To the extent possible, sponsors should use a single version of the selected convention or dictionary without revisions. However, if this is not possible, it is important to appropriately group and analyze adverse events taking into account the revisions in subsequent versions. It is not advisable to analyze adverse event data using one version and then base proposed labeling on a different version.

1. Accuracy of Coding

Sponsors should explore the accuracy of the coding process with respect to both investigators and the persons who code adverse events.

- Investigators may sometimes choose verbatim terms that do not accurately communicate the adverse event that occurred.
- The severity or magnitude of an event may be inappropriately exaggerated (e.g., if an investigator terms a case of isolated elevated transaminases acute liver failure despite the absence of evidence of associated hyperbilirubinemia, coagulopathy, or encephalopathy, which are components of the standard definition of acute liver failure).
- Conversely, the significance or existence of an event may be masked (e.g., if an investigator uses a term that is nonspecific and possibly unimportant to describe a subject's discontinuation from a study when the discontinuation is due to a serious adverse event).

If an adverse event is mischaracterized, sponsors could consider, in consultation with FDA, recharacterizing the event to make it consistent with accepted case definitions. We recommend that recharacterization be the exception rather than the rule and, when done, be well documented with an audit trail.

- We recommend that in addition to ensuring that investigators have accurately characterized adverse events, sponsors confirm that verbatim terms used by investigators have been appropriately coded.

Sponsors should strive to identify obvious coding mistakes as well as any instances when a potentially serious verbatim term may have been inappropriately mapped to a more benign coding term, thus minimizing the potential severity of an adverse event. One example is coding the verbatim term facial edema (suggesting an allergic reaction) as the nonspecific term edema; another is coding the verbatim term suicidal ideation as the more benign term emotional lability.

- Prior to analyzing a product's safety database, sponsors should ensure that adverse events were coded with minimal variability across studies and individual coders.

Consistency is important because adverse event coding may be performed over time, as studies are completed, and by many different individuals. Both of these factors are potential sources of variability in the coding process. FDA recommends that to examine the extent of variability in the coding process, sponsors focus on a subset of preferred terms, particularly terms that are vague and commonly coded differently by different people. For example, a sponsor might evaluate the consistency of coding

verbatim terms such as weakness and asthenia or dizziness and vertigo. NOS (not otherwise specified)-type codes, such as ECG abnormality NOS, are also coding terms to which a variety of verbatim terms may often be mapped. These should be examined for consistency as well. Sponsors should pay special attention to terms that could represent serious or otherwise important adverse reactions.

In addition to considering an adverse event independently and as it is initially coded, sponsors should also consider a coded event in conjunction with other coded events in some circumstances. Certain adverse events or toxicities (particularly those with a constellation of symptoms, signs, or laboratory findings) may be defined as an amalgamation of multiple preferred coding terms. Sponsors should identify these events (e.g., acute liver failure) based on recognized definitions.

2. Coding Considerations During Adverse Event Analysis

When analyzing an adverse event, sponsors should consider the following:

- Combining related coding terms can either amplify weak safety signals or obscure important toxicities.

For example, the combination of dyspnea, cough, wheezing, or pleuritis might provide a more sensitive, although less specific, appraisal of pulmonary toxicity than any single term. Conversely, by combining terms for serious, unusual events with terms for more common, less serious events (e.g., constipation might include cases of toxic megacolon), the more important events could be obscured.

- Coding methods can divide the same event into many terms. Dividing adverse event terms can decrease the apparent incidence of an adverse event (e.g., including pedal edema, generalized edema, and peripheral edema as separate terms could obscure the overall finding of fluid retention).

Although potentially important safety events cannot always be anticipated in a clinical development program, sponsors, in consultation with the Agency, should prospectively group adverse event terms and develop case definitions or use accepted standardized definitions whenever possible.

- A prospective grouping approach is particularly important for syndromes such as serotonin syndrome, Parkinsonism, and drug withdrawal, which are not well characterized by a single term.
- Some groupings can be constructed only after safety data are obtained, at which time consultation with FDA might be considered.
- Sponsors should explain such groupings explicitly in their applications so that FDA reviewers have a clear understanding of what terms were grouped and the rationale for the groupings.
- For safety signals that are identified toward the end of a development program, the pre-NDA meeting would be a reasonable time to confer with FDA regarding such groupings or case definitions.

B. Analyzing Temporal or Other Associations

For individual safety reports, the temporal relationship between product exposure and adverse event is a critical consideration in the assessment of potential causality. However, temporal factors, including the duration of the event itself, are often overlooked during the assessment of aggregate safety data. Simple comparisons of adverse event frequencies between (or among) treatment groups, which are commonly included in product applications and reproduced in tabular format in labeling, generally do not take into account the time dependency of adverse events. Temporal associations can help further understand causality, adaptation, and tolerance, but may be obscured when only frequencies of adverse events are compared.

Temporal analyses may be warranted for important adverse events whether they arise from controlled clinical trial data or treatment cohorts. In both cases, analyzing changes over time may be important for assessing risk and potential causality. Analyses of temporal associations are particularly worth conducting in situations where prior experience (e.g., experience from similar products) has shown that a temporal relationship between product exposure and ensuing adverse events is likely to exist. In addition, in the context of controlled clinical trials, temporal analyses may provide insight into the relative importance of differences in adverse event frequencies between study groups.

Descriptions of risk as a function of subjects' duration of exposure to a product, or as a function of time since initial exposure, can contribute to the understanding of the product's safety profile. Assessments of risk within discrete time intervals over the observation period (i.e., a hazard rate curve)

can be used to illustrate changes in risk over time (e.g., flu-like symptoms with interferons that tend to occur at the initiation of treatment but diminish in frequency over time). It may be useful for sponsors to consider event rates (events per unit of time) in reconciling apparent differences in the frequencies of events between studies when there are disparities in subjects' time of exposure or time at risk.

For important events that do not occur at a constant rate with respect to time and for events in studies where the size of the population at risk (denominator) changes over time, a life-table or Kaplan-Meier approach may be of value for evaluating risks of adverse events. Clinically important events (e.g., those events for which the occurrence of even a few cases in a database may be significant) are of particular interest. Examples of such events include the development of restenosis following coronary angioplasty, cardiac toxicity, and seizures.

Temporal associations identified in previous experience with related products can help focus sponsor analyses of potential temporal associations for a product under study, but sponsors should balance this approach with an attempt to detect unanticipated events and associations as well. Knowledge of a product's pharmacokinetic and pharmacodynamic profiles, as well as an appreciation of physiologic, metabolic, and host immune responses, may be important in understanding the possible timing of treatment-related adverse events.

It is important to consider study and concomitant treatment regimens (i.e., single treatment; short course of treatment; continuous, intermittent, titrated, or symptom-based treatment) in temporal analyses. Other important factors to consider in planning and interpreting temporal analyses are

(1) the initiation or withdrawal of therapies and (2) changes in the severity or frequency of subjects' preexisting conditions over time. For events that decrease in frequency over time and are found to be associated with the initiation of treatment, supplemental analyses may be of value to discriminate the relative contributions of adaptation, tolerance, dose reduction, symptomatic treatment, decreases in reporting, depletion of susceptibles, and subject dropout.

C. Analyzing Dose Effect as a Contribution to Risk Assessment

Sponsors should analyze event rates by dose for clinically important adverse events that may be product related and events that might be expected based on a product's pharmacologic class or pre-clinical data.

For studies involving the evaluation of a range of doses, dose response is most commonly assessed by analyzing adverse event frequencies by administered dose. In such studies, it may also be useful to consider event frequencies by weight-adjusted or body surface area-adjusted dose, especially if most patients are given the same dose regardless of body weight or size. It should be recognized, however, that when doses are adjusted by a subject's weight or body surface area, women are commonly overrepresented on the upper end of the range of adjusted doses, and men are commonly overrepresented on the lower end of this range. For products administered over prolonged periods, it may be useful to analyze event rates based on cumulative dose. In addition, when specific demographic or baseline disease-related subgroups may be at particular risk of incurring adverse events, exploration of dose-response relationships by subgroup is

important. Subgroup analyses have the potential to provide a more reliable and relevant estimate of risk for important subgroups of the target population. Alternatively, multiplicity issues could result in an apparent signal that does not represent a real finding (i.e., a false positive).

Although the most reliable information on dose response comes from randomized fixed dose studies, potentially useful information may emerge from titration studies and from associations between adverse events and plasma drug concentrations.

For dose titration or flexible dose studies, it would generally be useful to assess the relationship between adverse event frequencies and the actual doses subjects received preceding the adverse events or the cumulative dose they received at the onset of the events. The choice is a function of the mode of action, pharmacokinetics, and pharmacodynamics of the product.

For products with a stepped dosing algorithm (i.e., incremental dosing based on age or weight), the actual cut points of the paradigm are often selected relatively early in product development. Although the cut points may be based on the best knowledge available at the time, it is useful in such cases to make a specific effort to explore safety (and efficacy) just above and below these points. For example, if the dose of a product is to be 100 mg for patients weighing less than 80 kg and 150 mg for patients weighing 80 kg or more, an assessment of the comparative safety profiles of patients weighing from 75 to 79.9 kg versus patients weighing from 80 to 84.9 kg would be valuable.

As is typical of most safety evaluations, the likelihood of observing false positive signals increases

with the number of analyses conducted. Positive associations between adverse events and dose, as well as signals that emerge from subgroup analysis, should be considered with this in mind. Such associations should be examined for consistency across studies, if possible.

D. Role of Data Pooling in Risk Assessment

Data pooling is the integration of patient-level outcome data from several clinical studies to assess a safety outcome of interest. Generally, data pooling is performed to achieve larger sample sizes and data sets because individual clinical studies are not designed with sufficient sample size to estimate the frequency of low incidence events or to compare differences in rates or relative rates between the test drug (exposed group) and the control (unexposed group). Use of pooled data does not imply that individual study results should not be examined and considered. When pooling data, sponsors should consider the possibility that various sources of systematic differences can interfere with interpretation of a pooled result. To ensure that pooling is appropriate, sponsors should confirm that study designs, as well as ascertainment and measurement strategies employed in the studies that are pooled, are reasonably similar.

Used appropriately, pooled analyses can enhance the power to detect an association between product use and an event and provide more reliable estimates of the magnitude of risk over time. Pooled analyses can also provide insight into a positive signal observed in a single study by allowing a broader comparison. This can protect against undue weight being given to chance findings in individual studies. However, a finding from a single study should not be automatically dismissed because of the results

of a pooled analysis, especially if it is detected in a study of superior design or in a different population. Any pooled analysis resulting in a reduced statistical association between a product and an observed risk or magnitude of risk, as compared to the original safety signal obtained from one or more of the contributing studies, should be carefully examined.

Some issues for consideration in deciding whether pooling is appropriate include possible differences in the duration of studies, heterogeneity of patient populations, and case ascertainment differences across studies (i.e., different methods for detecting the safety outcomes of interest, such as differences in the intensities of patient follow-up). When there is clinical heterogeneity among trials with regard to the safety outcome of interest (e.g., major disparity in findings for particular safety endpoints), sponsors should present risk information that details the range of results observed in the individual studies, rather than producing a summary value from a pooled analysis.

E. Using Pooled Data for Risk Assessment

All placebo-controlled studies in a clinical development program should be considered and evaluated for appropriateness for inclusion in a pooled analysis. Decisions to exclude certain placebo-controlled studies from, or to add other types of studies (such as active-controlled studies or open-label studies) to, a pooled analysis would depend on the objectives of the analysis. Such analyses should be conducted in a manner that is consistent with the following guiding principles:

- Generally, phase 1 pharmacokinetic and pharmacodynamic studies should be excluded.

These are usually single- or multiple-dose trials of a short duration conducted in healthy subjects or in patients with refractory or incurable end-stage disease who have confounding symptoms. Unless a risk were limited to a short period immediately after the first dose, inclusion of these studies in a pooled analysis would not increase the statistical power or contribute to the precision of the risk estimates. However, inclusion of these studies could (1) diminish the magnitude of apparent risk by including a population with little or no possibility of having had the adverse reaction or (2) increase the apparent magnitude of risk because of significant baseline symptoms unrelated to the drug.

- The risk of the safety outcome of interest should be expressed in reference to total person-time (exposure time) or be evaluated using a time-to-event analysis.

When the duration of drug exposure for the individual subjects included in a pooled analysis varies, sponsors should not express the risk merely in terms of event frequency (that is, using persons as the denominator). Use of the person-time approach relies on the assumption that the risk is constant over the period of the studies. Whenever there is concern regarding a non-constant nature of a risk, a time-to-event log-rank type analysis may be helpful, as it is a robust approach even when risk is not constant over time.

- The patient population in the pooled analysis should be relatively homogeneous with respect to factors that may affect the safety outcome of interest (e.g., dose received, duration of therapy).

The pooled analysis should be of a size sufficient to allow analyses of demographic subgroups (gender, age, race, geographic locations).

- The studies included in a pooled analysis should have used similar methods of adverse event ascertainment, including ascertainment of the cause of dropouts.

Study-specific incidence rate should be calculated and compared for any signs of case ascertainment differences. Since study-to-study variation is to be expected, it is a challenge to distinguish between possible case ascertainment differences and study-to-study variation.

There are some situations in which pooling may be relatively straightforward. For example, a pooled analysis of similarly designed phase 3 studies could readily be used to create a table of common adverse events. This type of analysis is typically less subject to the problems discussed above because (1) the studies are similar in study design and patient population and (2) the intent of such an analysis is often more descriptive than quantitative. However, if a specific safety concern is raised during the clinical development program, the guiding principles discussed above should be closely followed when conducting a prespecified pooled analysis.

F. Rigorous Ascertainment of Reasons for Withdrawals from Studies

Subjects may drop out or withdraw from clinical trials for many reasons, including perceived lack of efficacy, side effects, serious adverse events, or an unwillingness to expend the effort necessary to continue. The reasons for dropout are not always clear. This lack of information may be largely irrel-

evant (e.g., discontinuation due to moving from the area) or indicative of an important safety problem (e.g., stroke). Therefore, regardless of the reason for withdrawal, sponsors should attempt to account for all dropouts.

- Sponsors should try to ascertain what precipitated dropout or withdrawal in all cases, particularly if a safety issue was a part of the reason for withdrawal.
- It is not helpful to simply record vague explanations such as “withdrew consent,” “failed to return,” “administratively withdrawn,” or “lost to follow-up.”
- Participants who leave a study because of serious or significant safety issues should be followed closely until the adverse events are fully and permanently resolved or stabilized (if complete resolution is not anticipated), with follow-up data recorded in the case report forms.
- Follow-up information should be pursued on patients withdrawn from the study (for reasons other than withdrawing consent in the absence of an adverse event).

If this information is not obtainable, FDA recommends that the measures taken to obtain follow-up information be reflected on the case report forms and the resultant failure to obtain the information should be discussed in the clinical discussion of safety.

- Patients considering withdrawing consent should be encouraged to provide the reason, and patients who withdraw should be

encouraged to provide information as to whether the withdrawal of consent resulted from a serious or significant safety issue.

- Some patients withdraw due to abnormal laboratory values, vital signs, or ECG findings that are not characterized as adverse events. Sponsors should include information on these types of discontinuations in addition to information on discontinuations due to adverse events.

G. Long-term Follow-up

In some cases, it is recommended that all subjects be followed to the end of the study or even after the formal end of the study (e.g., where the drug has a very long half-life, is deposited in an organ such as bone or brain, or has the potential for causing irreversible effects, such as cancer). The concern over adequate follow-up for ascertaining important safety events in such cases is particularly critical in long-term treatment and clinical outcome studies. In such cases, FDA recommends the follow-up for late safety events, even for subjects off therapy, include those subjects who drop out of the trial or who finish the study early due to meeting a primary outcome of interest. The duration of follow-up, however, would be dependent on the circumstances of the product development and therefore should be discussed with the appropriate review division (e.g., during end-of-phase 2 meetings).

H. Important Aspects of Data Presentation

We recommend that once a product's safety data have been analyzed, comprehensive risk assessment information be presented succinctly. FDA and ICH have provided extensive guidance regarding

the presentation of safety data,[13],[14], [15]and we offer these additional recommendations, which have not been addressed previously.

- For selected adverse events, adverse event rates using a range of more restrictive to less restrictive definitions (e.g., myocardial infarction versus myocardial ischemia) should be summarized.

The events chosen for such a summary might be limited to more serious events and events that are recognized to be associated with the relevant class of drugs;

- For a drug that is a new member of an established class of drugs, the adverse events that are important for the class of drug should be fully characterized in the NDA's integrated summary of safety.

That characterization should include an analysis of the incidence of the pertinent adverse events, as well as any associated laboratory, vital sign, or ECG data. For example, the characterization of a drug joining a class that is associated with orthostatic hypotension would include analyses of orthostatic blood pressure changes as well as the incidence of syncope, dizziness, falls, or other events. We recommend that when sponsors are establishing case definitions for particular adverse events, they consider definitions previously used for the other drugs in the class or, if available, standard definitions.

- The distribution of important variables across the pooled data, such as gender, age, extent of exposure, concomitant medical conditions, and concomitant medications (especially those that are used commonly to treat the

indication being studied), should be included in the integrated summary of safety.

- The effect of differential discontinuation rates by treatment on adverse event occurrence should be characterized (e.g., when placebo-treated patients drop out of a trial earlier than patients being treated with an active drug). This differential discontinuation can lead to misleading adverse event incidences unless patient exposure is used as the denominator for risk calculations.
- Case report forms (CRFs) submitted for patients who died or discontinued a study prematurely due to an adverse event should include copies of relevant hospital records, autopsy reports, biopsy reports, and radiological reports, when feasible. The possibility that such information may be reported to FDA should be stated in the informed consent document with a notation that the patient would not be identified in such reports.

These source documents should become a formal part of the official CRF and be properly referenced.

- Narrative summaries (as previously described in guidance[16]) of important adverse events (e.g., deaths, events leading to discontinuation, other serious adverse events) should provide the detail necessary to permit an adequate understanding of the nature of the adverse event experienced by the study subject. (This level of detail may be unnecessary for events expected in the population (e.g., late deaths in a cancer trial). This issue should be discussed with the appropriate review division.)

Narrative summaries should not merely provide, in text format, the data that are already presented in the case report tabulation, as this adds little value. A valuable narrative summary would provide a complete synthesis of all available clinical data and an informed discussion of the case, allowing a better understanding of what the patient experienced. The following is a list of components that would be found in a useful narrative summary:

- Patient age and gender
- Signs and symptoms related to the adverse event being discussed
- An assessment of the relationship of exposure duration to the development of the adverse event
- Pertinent medical history
- Concomitant medications with start dates relative to the adverse event
- Pertinent physical exam findings
- Pertinent test results (e.g., lab data, ECG data, biopsy data)
- Discussion of the diagnosis as supported by available clinical data
- For events without a definitive diagnosis, a list of the differential diagnoses
- Treatment provided
- Re-challenge results (if performed)
- Outcomes and follow-up information

Notes

[1] This guidance has been prepared by the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration.

[2] For ease of reference, this guidance uses the terms product and drug to refer to all products (excluding blood and blood components) regulated by CDER or CBER, including vaccines. Similarly, for ease of reference, this draft 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).

[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>

[4] Section 505(d)(1) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(d)(1)) requires the conduct of “adequate tests by all methods reasonably applicable to show whether or not . . . [a] drug is safe for use under the [labeled] conditions. . . .” See also 21 CFR 314.50(d)(5)(vi). Section 351 of the Public Health Service Act (42 U.S.C. 262) requires a demonstration that a biologic is “safe, pure, and potent.” See also 21 CFR 601.2.

[5] See the guidance for industry E1A The Extent of Population Exposure to Assess Clinical Safety: For Drugs Intended for Long-Term Treatment of Non-Life-Threatening Conditions, International Conference on Harmonisation (ICH).

[6] See the guidance for industry E1A The Extent of Population Exposure to Assess Clinical Safety: For Drugs Intended for Long-term Treatment of Non-Life-Threatening Conditions, ICH.

[7] The memorandum from Janet Woodcock, M.D., to Michael Friedman, M.D., dated July 20, 1998, and titled FDAMA – Women and Minority Guidance Requirements (with its attached report) discusses the regulations related to diversity. The memorandum can be found on the CDER guidance page under Modernization Act guidance <http://www.fda.gov/cder/guidance/women.pdf>

[8] See FDA’s guidance for industry Exposure-Response Relationships — Study Design, Data Analysis, and Regulatory Applications.

[9] The Pharmacovigilance Guidance discusses additional risk assessment strategies that may be initiated either pre- or postapproval. In particular, the Pharmacovigilance Guidance includes a detailed discussion of pharmacoepidemiologic safety

studies. Although such studies would principally be initiated after marketing, the Pharmacovigilance Guidance discusses certain situations when they could be initiated preapproval.

[10] As mentioned in the RiskMAP Guidance, an LSSS could also be a method of evaluating the effectiveness of RiskMAP tools in actual practice prior to approval.

[11] Stamatis, D.H., Failure Mode and Effect Analysis: FMEA From Theory to Execution, Milwaukee: American Society for Quality, Quality Press, 2003.

[12] Cohen, Michael R. ed., Medication Errors: Causes, Prevention, and Risk Management, Washington D.C.: American Pharmaceutical Association, 1999.

[13] See Guideline for the Format and Content of the Clinical and Statistical Section of an Application.

[14] See the guidance for industry E3 Structure and Content of Clinical Study Reports, ICH.

[15] See the guidance for industry M4 Common Technical Document for the Registration of Pharmaceuticals for Human Use, ICH.

[16] See the guidance for industry E3 Structure and Content of Clinical Study Reports, ICH.
tated dropout or withdrawal in all cases, particularly if a safety issue was a part of the reason for withdrawal.

RISK MANAGEMENT

FDA Guidance for Industry

Development and Use of Risk Minimization Action Plans (RiskMAPs)

I. INTRODUCTION

This document provides guidance to industry on good risk assessment practices during the development of prescription drug products, including biological drug products.[2] This is one of three guidances that were developed to address risk management activities. Specifically, this document discusses the generation, acquisition, analysis, and presentation of premarketing safety data.

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

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 developing the three draft guidance documents on risk management activities. The draft guidance documents were published on May 5, 2004, and the public was provided with an opportunity to comment on them until July 6, 2004. FDA considered all of the comments received in producing the final guidance documents:

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 Guidance Documents

Like the concept papers and draft guidances that preceded them, each of the three final 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 (see e.g., FDA requirements for professional labeling and adverse event monitoring and reporting). As a result, many of the recommendations presented here focus on situations in which a product may pose a clinically important and unusual type or level of risk. To the extent possible, we have specified in the text whether a recommendation is intended for 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]

- To the extent possible, this guidance reflects FDA's commitment to harmonization of international definitions and standards.
- When planning risk assessment and risk minimization activities, sponsors should consider input from healthcare participants likely to be affected by these activities (e.g., from consumers, pharmacists and pharmacies, physicians, nurses, and 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 in section II.B, FDA views risk management as an iterative process encompassing the assessment of risks and benefits, the minimization of risks, and the maximization of benefits. Specifically, 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 to define 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). Efforts to maximize benefits to improve the overall balance of risks and benefits can be pursued in concert with risk minimization efforts and can be discussed with FDA.

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. Benefits and risks are difficult to quantify and compare because they may apply to different individuals and are usually measured

and valued differently. Examples of factors to weigh are (1) population risks and benefits, (2) individual benefits from treatment, (3) risks of nontreatment or alternative products, and (4) modest population benefits in the context of a serious adverse effect that occurs rarely or unpredictably. Benefits as well as risks are also patient-specific and are influenced by such factors as (1) the severity of the disease being treated, (2) the outcome of the disease if untreated, (3) the probability and magnitude of any treatment effect, (4) existing therapeutic options, and (5) the individual's understanding of risks and benefits and the value they attach to each of them. Thus, assessment and comparison of a product's benefits and risks is a complicated process that is influenced by a wide range of societal, healthcare, and individualized patient 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 communication of risks and benefits through product labeling is the cornerstone of risk management efforts for prescription drugs. [4] For most prod-

ucts, routine risk management will be sufficient and a RiskMAP need not be considered.

There are, however a small number of products for which a RiskMAP should be considered (see section III.D). 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.

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] A RiskMAP could also be considered as a selectively used type of Safety Action Plan as defined in the International Conference on Harmonization (ICH) guidance E2E: Pharmacovigilance Planning (E2E guidance).[6]

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, is a statement of 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, a goal may be the elimination of dangerous concomitant prescribing. The objectives could include lowering physician co-prescribing rates and/or pharmacist co-dispensing rates. 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 to communicate risks and appropriate safety behaviors to healthcare 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

For certain types of risks (e.g., teratogenicity of category X drug products), it may be possible to develop systems with similar processes and procedures that can be used industrywide.

The use of these systems can occur outside of a RiskMAP. For example, while most drugs do not need a RiskMAP, many would still benefit from a program of physician and patient education and outreach. At times, communication of potential product risks may be warranted before a sponsor agrees to do a RiskMAP or an agreed upon RiskMAP is completed.

D. Determining When a RiskMAP Should Be Considered[7]

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.[8] 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.

Although it is expected and hoped that sponsors will determine when a RiskMAP would be appropriate, FDA may recommend a RiskMAP based on the Agency's own interpretation of risk information.

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 effects and 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 their risks and benefits; and (4) reversibility of adverse events observed.

- Preventability of adverse effects: Serious adverse effects that can be minimized or avoided by preventive measures around drug prescribing are the preferred candidates for RiskMAPs.
- Probability of benefit: If factors are identified that can predict effectiveness, a RiskMAP could help encourage appropriate use to increase benefits relative to known risks.

Consider the following examples:

- 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.
- Drugs that provide important benefits, but that are human teratogens would often be appropriate for a RiskMAP to minimize in utero exposure.

- Some drugs may warrant RiskMAP consideration because safe and effective use call for specialized healthcare skills, training, or facilities to manage the therapeutic or serious side effects of the drug.

Involving all stakeholders during the initial phases of considering whether a RiskMAP is appropriate allows input and buy-in by all parties who will later have roles in implementing the RiskMAP. If a RiskMAP is appropriate, stakeholders can help shape the RiskMAP to foster its success in the healthcare delivery environment. Therefore, we recommend public discussion about the appropriateness of a RiskMAP through the FDA advisory committee process. Such public advisory committee meetings can also be used to address (1) whether a RiskMAP is appropriate, (2) what the goals and objectives of the RiskMAP could be (see footnote 6), (3) the circumstances under which a RiskMAP tool might be revised or terminated, and (4) whether a RiskMAP itself is no longer appropriate. The FDA advisory committee structure and processes are well suited to foster such discussions as they arise on a case-by-case basis.

IV. TOOLS FOR ACHIEVING RISKMAP GOALS AND OBJECTIVES

A risk minimization tool is a process or system intended to minimize known risks. 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 situations or patient populations. A number of tools are available; 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 are directed at the overall RiskMAP goal or goals. One or more tools can be chosen to achieve a particular objective. For example, a 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, before receiving the product, the patient formally acknowledges their understanding and/or agreement not to take product B 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 the use of tools in different categories does not imply greater or lesser safety risks, but rather indicates the particular circumstances put in place to achieve the objectives and goals.

1. Targeted Education and Outreach

FDA recommends that sponsors consider tools in the targeted education and outreach category (1) when routine risk minimization is known or likely to be insufficient to minimize product risks 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 about risks to increase appropriate knowledge and behaviors of key people or groups (e.g., healthcare practitioners and consumers) that have the capacity to prevent or mitigate the product risks of concern.

FDA acknowledges that tools in this category are occasionally used for products where the benefit/risk balance does not necessarily warrant a RiskMAP. Educational efforts by sponsors might include one or more of the tools described below without a RiskMAP being in place. Sponsors are encouraged to continue using tools, such as education and outreach, as an extension of their routine risk minimization efforts even without a RiskMAP.

Examples of tools in this category are as follows:

- healthcare practitioner letters
- training programs for healthcare practitioners or patients
- continuing education for healthcare practitioners such as product-focused programs developed by sponsors and/or sponsor-supported accredited CE programs

- prominent professional or public notifications
- patient labeling such as Medication Guides and patient package inserts
- promotional techniques such as direct-to-consumer advertising highlighting appropriate patient use or product risks
- patient-sponsor interaction and education systems such as disease management and patient access programs

In addition to informing healthcare 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 known or likely to be insufficient to minimize identified risks.

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

- Patient education that includes acknowledgment of having read the material and an agreement to follow instructions. These agreements are sometimes called consent forms.
- Healthcare provider training programs that include testing or some other documentation of physicians' knowledge and understanding.
- Enrollment of physicians, pharmacies, and/or patients in special data collection systems that also reinforce appropriate product use.
- Limited number of doses in any single prescription or limitations on refills of the product.
- Specialized product packaging to enhance safe use of the product.
- Specialized systems or records that are used to attest that safety measures have 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. Tools in this category, because they are very burdensome and can disrupt usual patient care, should be considered

only 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 known or likely to be 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 (e.g., the product is not made available unless there is an agreement or acknowledgment, documented qualifications, enrollment, and/or appropriate testing or laboratory records)
- prescription only by specially certified healthcare practitioners
- product dispensing limited to pharmacies or practitioners that elect to be specially certified
- product dispensing only to patients with evidence or other documentation of safe-use conditions (e.g., lab test results)

Performance-linked access systems should seek to avoid unnecessary or unintended restrictions or fragmentation of healthcare services that may limit access by physicians, pharmacists, or patients, or that may lead to discontinuities in medical or pharmacy care.

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. On the contrary, FDA does not suggest that the tools listed on the Web site are the only tools that could be useful and encourages sponsors to develop tools that may be optimal for their particular products. See also Section V.D on making information from RiskMAP evaluations available to the public.

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 healthcare 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 and outreach would likely be sufficient).
- Identify the key stakeholders who have the capacity to minimize the product's risks (such as physicians, pharmacists, pharmacies, nurses, patients, and third-party payers) and define the anticipated role of each group.
- Seek input from the key stakeholders on the feasibility of implementing and accepting the tool in usual healthcare practices, disease conditions, or lifestyles, if possible. Examples of considerations could include (but would not be limited to) patient and healthcare 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 healthcare relationships.
- Design the RiskMAP to be:
 1. compatible with current technology
 2. applicable to both outpatient and inpatient use
 3. accessible to patients in diverse locales, including non-urban settings
 4. consistent with existing tools and programs, or

systems that have been shown to be effective with similar products, indications, or risks

- Select tools based on available evidence of effectiveness in achieving the specified objective (e.g., tools effectively used in p regnancy 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 healthcare practitioner behaviors in medical care settings).
- Consider, and seek to avoid, unintended consequences of tool implementation that obstruct risk minimization and product benefit, such as obstructing patient access or driving patients to seek alternative product sources (e.g., Internet sales, counterfeit products) or less appropriate products.

FDA recognizes that once it approves a product for marketing, healthcare practitioners are the most important managers of product risks. FDA believes that by including information in the FDA-approved professional labeling on the conditions in which medical products can be used safely and effectively by their intended population and for their intended use or uses, the Agency and the sponsor encourage healthcare 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 healthcare practitioners to

prescribe products for conditions other than those described in FDA-approved professional labeling, or to otherwise regulate medical or surgical practice.

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 (see e.g., FDA requirements for professional labeling and adverse event monitoring and reporting).

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. RiskMAPs and their

component objectives and tools should be monitored and evaluated in a timely manner 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 Healthcare 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 that every RiskMAP contain a plan for periodically evaluating its effectiveness after implementation (see section VII for a detailed discussion of RiskMAP submissions to FDA).[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 healthcare 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. The specific types of data gathered in a RiskMAP evaluation will determine whether it would be appropriate to include a statistical analysis of evaluation results.

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. 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 outcome from product use, a sample performance measure could be the complication rate. For evaluation purposes, a target for that measure could be established to be no more than a specified number or rate of that complication. In some cases, however, 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 test results for

determining if pregnancy occurred). The sensitivity, specificity, and predictive value of surrogate markers should be established before their use as a performance measure.

- Process measures that reflect desirable safety behaviors (e.g., performance of recommended laboratory monitoring, signatures attesting to knowledge or discussions of risk).
- 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 is to the RiskMAP goal, the greater its degree of validity. For example, if the RiskMAP goal is avoidance of liver failure, then ascertainment of the rate of liver failure in the user population would be a highly valid performance measure. Hospitalization for severe liver injury would be another, but less direct, assessment of the RiskMAP goal. The frequency of liver function monitoring in users could be used to see if RiskMAP processes to prevent liver failure were being followed, but since liver function monitoring may not be tightly linked to the occurrence of liver failure, such process monitoring would have limited validity as an indicator of successful prevention of liver failure.

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 or active surveillance of adverse events in populations with well-defined exposure to the product would be preferred 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 may come from various insurers, purchasing groups, or networks that are tied to employment or entitlement programs, so it is important to determine if an administrative data system is representative of the general population being treated with the product. 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] In addition, there may be data processing time lags of several months or longer before administrative data can be retrieved and analyzed.

- 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 healthcare 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 healthcare 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]

These examples illustrate how using only one evaluation 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, surveys of healthcare practitioners may indicate high compliance with systems for preventing product complications. However, systematically collected or spontaneous reports might show that product complications are occurring, thus suggesting that prevention efforts in actual practice may be ineffective or incompletely applied. 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. If RiskMAPs use multiple tools or interventions, it may be useful to consider using evaluation methods applicable to the program as a whole. For example, a systematic program evalu-

ation model, such as Failure Modes and Effect Analysis (FMEA),[13], [14] can provide a framework for evaluating the individual RiskMAP components and the relative importance of each in achieving the overall RiskMAP goal or goals.

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 achievement of goals and the performance of 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 discon-

tinue a tool, whereas its converse may trigger the implementation of new or improved tools, or even a redesign of the overall RiskMAP. Two important factors that contribute to tool effectiveness are its acceptability and unintended consequences. Since tool performance will often depend upon the understanding, cooperation, efforts, and resources of healthcare providers, pharmacists, and patients, evaluation of acceptability and unintended consequences for individual tools may help to improve the use of tools and thus their performance.

4. Evaluating RiskMAP Tools Prior to Implementation

FDA recommends that, to the extent possible, sponsors evaluate tools for effectiveness before implementation. As discussed in section IV.D, FDA suggests that in selecting tools to include in a RiskMAP, a sponsor consider tools that are likely to 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. Application of computer modeling or simulation techniques may also assist in projecting potential outcomes of implementation of various combinations of RiskMAP tools.

Besides using literature evidence and past RiskMAP experience to identify tools with a known track record of effectiveness, sponsors can pretest or pilot test a tool before implementation. Such testing, ideally with a comparison group or time period, can help to assess comprehension, acceptance, feasibility, and other factors that influence how readily RiskMAP tools will fit into patient lifestyles and the everyday practices of healthcare practitioners. Pre-testing can potentially avoid wasted time, expense, and escalation of RiskMAP tools by discriminating

between high- and low-performing tools. For example, if a preventable risk is identified in Phase 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.[15] 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. In such instances, sponsors should seek to employ tools with a proven track record of effectiveness. In general, the greater the rate or severity of risks to be minimized, the more critical it becomes to have compelling evidence of effectiveness of the tool through some form of testing or prior use.

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 and the other risk management guidances. At a minimum, FDA and sponsors would discuss their respective RiskMAP evaluations in a meeting or teleconference. In cases where risks are frequent and/or severe, or where results are ambiguous or uncertain, or where there is disagreement between the sponsor and FDA in the interpretation of the RiskMAP or tool effectiveness, public and expert input would be sought through the FDA Advisory Committee process. This will also allow airing and discussion of important information about effective and ineffective RiskMAPs and tools.

D. Making Information From RiskMAP Evaluations Available to the Public

As discussed in section IV.C, FDA plans to maintain a RiskMAP Web site that will describe all publicly available information about implemented RiskMAPs (and their tools). On the same Web site, FDA intends to make available, in summary format, information that has been publicly discussed or is otherwise publicly available (from sponsors or other sources) about the effectiveness of particular RiskMAP tools in achieving risk minimization objectives. The sum-

maries may derive from materials presented and discussed at FDA Advisory Committee meetings where the effectiveness of a particular RiskMAP has been discussed and potential modifications have been entertained.

VI. COMMUNICATING WITH FDA REGARDING RiskMAP DEVELOPMENT AND DESIGN ISSUES

As discussed in section III.D, because risk and benefit information emerge continually throughout a product's lifecycle, a sponsor could decide, or FDA could recommend, that a RiskMAP is appropriate at several different times. These times include:

- before approval, when a risk is identified from clinical studies, nonclinical studies, or in similar class of products, 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 review division is the primary contact for a sponsor. The review division may choose to consult with other Offices in assisting the sponsor in developing a RiskMAP. These consulting offices could include CDER's Office of Drug Safety

(ODS), CBER's Office of Biostatistics and Epidemiology (OBE), or CDER's Office of Generic Drugs (OGD), as appropriate. In any particular case, it is 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 their targets, 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.

Both CDER and CBER will develop internal Manuals of Policies and Procedures (MaPPs) (or standard operating procedures (SOPs)) regarding the review of RiskMAPs. The procedures will define milestone points at which RiskMAP discussion is logical and will promote consistency in RiskMAP review and design. All RiskMAPs involving reminder tools or performance-linked access systems will be considered at the Center level as a secondary method of ensuring consistency across product classes and across divisions.

If the sponsor decides to submit a RiskMAP before marketing approval of the product, most times the RiskMAP will be submitted to the new drug application (NDA) or biologics license application (BLA) for the product in question. However, if a risk is identified early (e.g., the product is a teratogen), and the sponsor wishes to institute formal risk management activities during Phases 1 to 3 studies, the sponsor can submit the RiskMAP to the investigational new drug application (IND). 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. Additional user fees will only be applicable to a supplement if FDA determines that new clinical data are required for its approval. This would be unlikely for a RiskMAP supplement.

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.

VII. Recommended Elements of a RISKMAP SUBMISSION TO FDA

A. Contents of a RiskMAP Submission to FDA

FDA suggests that a RiskMAP submission to FDA include the following sections, as well as a table of contents:

- Background
- Goals and Objectives

- Strategy and Tools
- Evaluation Plan

- Is the risk time-limited, continuous, or cumulative?

1. Background

FDA suggests that the Background section explain why a RiskMAP is being considered and created. We recommend that it describe the risks to be minimized and the benefits that would be preserved by implementation of a RiskMAP. Further, we suggest that this section describe, to the extent possible, the type, severity, frequency, and duration of the product's risks, with particular attention to the risk or risks addressed by the RiskMAP.

The following are sample questions regarding risk characterization that we recommend be addressed in the Background section:

- What is the rationale for the RiskMAP?
- What is the risk the RiskMAP addresses?
Is there more than one risk to be minimized?
If there is, how do they relate to each other with regard to the following bulleted items?
- What is the magnitude and severity of the risk?
- Who is at highest risk?
- Are particular populations at risk (e.g., children, pregnant women, the elderly)?
- Is the risk predictable?
- Is the risk preventable?
- Is the risk reversible?

These questions are similar in intent to what the ICH calls a Safety Specification in its E2E guidance.[16]

FDA recommends that this section include a discussion that considers the product's risks in the context of its benefits. The following are sample questions that address benefit characterization.

- What is the overall nature or extent of benefit and what are the expected benefits over time (i.e., long-term benefits)?
- How do the populations most likely to benefit from this product compare to those that may be at highest risk?
- 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 affect 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 healthcare, or sponsor actions in minimizing the risks of concern for this product. 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. We encourage sponsors to provide applicable information or evaluations from past experiences with products or programs that are similar to the proposed RiskMAP.

2. Goals and Objectives

FDA suggests that the Goals and Objectives section describe the goals and objectives of the RiskMAP.[17] 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 patient or healthcare interests, and if it did, we suggest that the sponsor describe the feedback that was received regarding the feasibility of its RiskMAP. FDA plans to maintain a Web site that will describe publicly available summary information about effectiveness of RiskMAP tools (see section V.D).

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.

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., ascertainment of outcomes, comprehension testing, patient surveys, process audits). FDA suggests that it describe the evaluation plan, sources of potential measurement error or bias for the outcome of interest, and any 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 for detecting differences where appropriate.

3. Data

To the extent possible, we recommend that the Data section of a RiskMAP progress report contain data that would allow FDA to analyze the information and make conclusions independently.

4. Results

To the extent possible, we recommend that the Results section of a RiskMAP progress report contain

the primary data from each evaluation method and analyses of the evaluation data, statistical estimation if appropriate, and the sponsor's comparison of tool, objective, and/or goal achievement relative to targeted performance measures.

5. Discussion and Conclusions

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

Progress towards achieving RiskMAP goals or performance measures should be reported. Where appropriate, sponsors are encouraged to propose modifications to the RiskMAP and discuss them with FDA.

Notes

[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).

[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>

[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).

[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 the healthcare 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] This ICH guidance is available on the Internet at <http://www.fda.gov/cder/guidance/index.htm> under the topic ICH Efficacy. The draft E2E guidance was made available on March 30, 2004 (69 FR 16579). ICH agreed on the final version of the E2E guidance in November 2004.

[7] This guidance is directed primarily toward sponsors of innovator products. However, a generic product may have the same benefit-risk balance as an innovator product and so may be considered for a similar RiskMAP.

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

[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.

[10] As noted in section III.B, 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 sponsor should consider submitting a formal evaluation plan.

[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.

[13] Stamatis DH, *Failure Mode and Effects Analysis: FMEA From Theory to Execution*, Milwaukee: American Society for Quality, Quality Press, 2003.

[14] Cohen Michael R ed, *Medication Errors: Causes, Prevention, and Risk Management*, Washington, DC: American Pharmaceutical Association, 1999.

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

[16] Available on the Internet at <http://www.fda.gov/cder/guidance/index.htm> under the topic ICH Efficacy.

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

RISK MANAGEMENT

FDA Guidance for Industry

Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment

I. INTRODUCTION

This document provides guidance to industry on good risk assessment practices during the development of prescription drug products, including biological drug products.[2] This is one of three guidances that were developed to address risk management activities. Specifically, this document discusses the generation, acquisition, analysis, and presentation of premarketing safety data.

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

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 developing three draft guidance documents on risk management activities. The draft guidance documents were published on May 5, 2004, and the public was provided with an opportunity to comment on them until July 6, 2004. FDA considered all of the comments received in producing the final guidance documents.

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 Guidances

Like the concept papers and draft guidances that preceded them, each of the three final 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 (see e.g., FDA requirements for professional labeling, and adverse event monitoring and reporting). As a result, many of the recommendations presented here focus on situations when a product may pose a clinically important and unusual type or level of risk. To the extent possible, we have specified in the text whether a recommendation is intended for 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]

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

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 input from health care participants likely to be affected by these activities (e.g., from consumers, pharmacists and pharmacies, physicians, nurses, and 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 PHARMACOVIGILANCE AND PHARMACOEPIDEMIOLOGY IN RISK MANAGEMENT

Risk assessment during product development should be conducted in a thorough and rigorous manner; however, it is impossible to identify all safety concerns during clinical trials. Once a product is marketed, there is generally a large increase in the

number of patients exposed, including those with co-morbid conditions and those being treated with concomitant medical products. Therefore, postmarketing safety data collection and risk assessment based on observational data are critical for evaluating and characterizing a product's risk profile and for making informed decisions on risk minimization.

This guidance document focuses on pharmacovigilance activities in the post-approval period. This guidance uses the term pharmacovigilance to mean all scientific and data gathering activities relating to the detection, assessment, and understanding of adverse events. This includes the use of pharmacoepidemiologic studies. These activities are undertaken with the goal of identifying adverse events and understanding, to the extent possible, their nature, frequency, and potential risk factors.

Pharmacovigilance principally involves the identification and evaluation of safety signals. In this guidance document, safety signal refers to a concern about an excess of adverse events compared to what would be expected to be associated with a product's use. Signals can arise from postmarketing data and other sources, such as preclinical data and events associated with other products in the same pharmacologic class. It is possible that even a single well-documented case report can be viewed as a signal, particularly if the report describes a positive rechallenge or if the event is extremely rare in the absence of drug use. Signals generally indicate the need for further investigation, which may or may not lead to the conclusion that the product caused the event. After a signal is identified, it should be further assessed to determine whether it represents a potential safety risk and whether other action should be taken.

IV. IDENTIFYING AND DESCRIBING SAFETY SIGNALS: FROM CASE REPORTS TO CASE SERIES

Good pharmacovigilance practice is generally based on acquiring complete data from spontaneous adverse event reports, also known as case reports. The reports are used to develop case series for interpretation.

A. Good Reporting Practice

Spontaneous case reports of adverse events submitted to the sponsor and FDA, and reports from other sources, such as the medical literature or clinical studies, may generate signals of adverse effects of drugs. The quality of the reports is critical for appropriate evaluation of the relationship between the product and adverse events. FDA recommends that sponsors make a reasonable attempt to obtain complete information for case assessment during initial contacts and subsequent follow-up, especially for serious events,[4] and encourages sponsors to use trained health care practitioners to query reporters. Computer-assisted interview technology, targeted questionnaires, or other methods developed to target specific events can help focus the line of questioning. When the report is from a consumer, it is often important to obtain permission to contact the health care practitioner familiar with the patient's adverse event to obtain further medical information and to retrieve relevant medical records, as needed.

FDA suggests that the intensity and method of case follow-up be driven by the seriousness of the event reported, the report's origin (e.g., health care practitioner, patient, literature), and other factors. FDA recommends that the most aggressive follow-up

efforts be directed towards serious adverse event reports, especially of adverse events not known to occur with the drug.

B. Characteristics of a Good Case Report

Good case reports include the following elements:

1. Description of the adverse events or disease experience, including time to onset of signs or symptoms;
2. Suspected and concomitant product therapy details (i.e., dose, lot number, schedule, dates, duration), including over-the-counter medications, dietary supplements, and recently discontinued medications;
3. Patient characteristics, including demographic information (e.g., age, race, sex), baseline medical condition prior to product therapy, co-morbid conditions, use of concomitant medications, relevant family history of disease, and presence of other risk factors;
4. Documentation of the diagnosis of the events, including methods used to make the diagnosis;
5. Clinical course of the event and patient outcomes (e.g., hospitalization or death);[5]
6. Relevant therapeutic measures and laboratory data at baseline, during therapy, and subsequent to therapy, including blood levels, as appropriate;
7. Information about response to dechallenge and rechallenge; and

8. Any other relevant information (e.g., other details relating to the event or information on benefits received by the patient, if important to the assessment of the event).

For reports of medication errors, good case reports also include full descriptions of the following, when such information is available:

1. Products involved (including the trade (proprietary) and established (proper) name, manufacturer, dosage form, strength, concentration, and type and size of container);
2. Sequence of events leading up to the error;
3. Work environment in which the error occurred; and
4. Types of personnel involved with the error, type(s) of error, and contributing factors.

FDA recommends that sponsors capture in the case narrative section of a medication error report all appropriate information outlined in the National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) Taxonomy.[6] Although sponsors are not required to use the taxonomy, FDA has found the taxonomy to be a useful tool to categorize and analyze reports of medication errors. It provides a standard language and structure for medication error-related data collected through reports.

C. Developing a Case Series

FDA suggests that sponsors initially evaluate a signal generated from postmarketing spontaneous

reports through a careful review of the cases and a search for additional cases. Additional cases could be identified from the sponsor's global adverse event databases, the published literature, and other available databases, such as FDA's Adverse Event Reporting System (AERS) or Vaccine Adverse Events Reporting System (VAERS), using thorough database search strategies based on updated coding terminology (e.g., the Medical Dictionary for Regulatory Activities (MedDRA)). When available, FDA recommends that standardized case definitions (i.e., formal criteria for including or excluding a case) be used to assess potential cases for inclusion in a case series.[7] In general, FDA suggests that case-level review occur before other investigations or analyses. FDA recommends that emphasis usually be placed on review of serious, unlabeled adverse events, although other events may warrant further investigation (see section IV.F. for more details).

As part of the case-level review, FDA suggests that sponsors evaluate individual case reports for clinical content and completeness, and follow up with reporters, as necessary. It is important to remove any duplicate reports. In assessing case reports, FDA recommends that sponsors look for features that may suggest a causal relationship between the use of a product and the adverse event, including:

1. Occurrence of the adverse event in the expected time (e.g., type 1 allergic reactions occurring within days of therapy, cancers developing after years of therapy);
2. Absence of symptoms related to the event prior to exposure;
3. Evidence of positive dechallenge or positive rechallenge;

4. Consistency of the event with the established pharmacological/toxicological effects of the product, or for vaccines, consistency with established infectious or immunologic mechanisms of injury;
5. Consistency of the event with the known effects of other products in the class;
6. Existence of other supporting evidence from preclinical studies, clinical trials, and/or pharmaco-epidemiologic studies; and
7. Absence of alternative explanations for the event (e.g., no concomitant medications that could contribute to the event; no co- or pre-morbid medical conditions).

Confounded cases are common, especially among patients with complicated medical conditions. Confounded cases (i.e., cases with adverse events that have possible etiologies other than the product of concern) could still represent adverse effects of the product under review. FDA recommends that sponsors carefully evaluate these cases and not routinely exclude them. Separate analyses of unconfounded cases may be useful.

For any individual case report, it is rarely possible to know with a high level of certainty whether the event was caused by the product. To date, there are no internationally agreed upon standards or criteria for assessing causality in individual cases, especially for events that often occur spontaneously (e.g. stroke, pulmonary embolism). Rigorous pharmaco-epidemiologic studies, such as case-control studies and cohort studies with appropriate follow-up, are usually employed to further examine the potential association between a product and an adverse event.

FDA does not recommend any specific categorization of causality, but the categories probable, possible, or unlikely have been used previously.[8] If a causality assessment is undertaken, FDA suggests that the causal categories be specified and described in sufficient detail to understand the underlying logic in the classification.

If the safety signal relates to a medication error, FDA recommends that sponsors report all known contributing factors that led to the event. A number of references are available to assist sponsors in capturing a complete account of the event.[9] FDA recommends that sponsors follow up to the extent possible with reporters to capture a complete account of the event, focusing on the medication use systems (e.g., prescribing/order process, dispensing process, administration process). This data may be informative in developing strategies to minimize future errors.

D. Summary Descriptive Analysis of a Case Series

In the event that one or more cases suggest a safety signal warranting additional investigation, FDA recommends that a case series be assembled and descriptive clinical information be summarized to characterize the potential safety risk and, if possible, to identify risk factors. A case series commonly includes an analysis of the following:

1. The clinical and laboratory manifestations and course of the event;
2. Demographic characteristics of patients with events (e.g., age, gender, race);
3. Exposure duration;

4. Time from initiation of product exposure to the adverse event;
5. Doses used in cases, including labeled doses, greater than labeled doses, and overdoses;
6. Use of concomitant medications;
7. The presence of co-morbid conditions, particularly those known to cause the adverse event, such as underlying hepatic or renal impairment;
8. The route of administration (e.g., oral vs. parenteral);
9. Lot numbers, if available, for products used in patients with events; and
10. Changes in event reporting rate over calendar time or product life cycle.

E. Use of Data Mining to Identify Product-Event Combinations

At various stages of risk identification and assessment, systematic examination of the reported adverse events by using statistical or mathematical tools, or so-called data mining, can provide additional information about the existence of an excess of adverse events reported for a product.

By applying data mining techniques to large adverse event databases, such as FDA's AERS or VAERS, it may be possible to identify unusual or unexpected product-event combinations warranting further investigation. Data mining can be used to augment existing signal detection strategies and is especially useful for assessing patterns, time trends, and events associated with drug-drug interactions.

Data mining is not a tool for establishing causal attributions between products and adverse events.

The methods of data mining currently in use usually generate a score comparing (1) the fraction of all reports for a particular event (e.g., liver failure) for a specific drug (i.e., the "observed reporting fraction") with (2) the fraction of reports for the same particular event for all drugs (i.e., "the expected reporting fraction").[10] This analysis can be refined by adjusting for aspects of reporting (e.g., the reporting year) or characteristics of the patient (e.g., age or gender) that might influence the amount of reporting. In addition, it may be possible to limit data mining to an analysis for drugs of a specific class or for drugs that are used to treat a particular disease.

The score (or statistic) generated by data mining quantifies the disproportionality between the observed and expected values for a given product-event combination. This score is compared to a threshold that is chosen by the analyst. A potential excess of adverse events is operationally defined as any product-event combination with a score exceeding the specified threshold. When applying data mining to large databases (such as AERS), it is not unusual for a product to have several product-event combinations with scores above a specified threshold. The lower the threshold, the greater the likelihood that more combinations will exceed the threshold and will warrant further investigation.

Several data mining methods have been described and may be worth considering, such as the Multi-Item Gamma Poisson Shrinker (MGPS) algorithm[11],[12], the Proportional Reporting Ratio (PRR) method[13],[14]and the Neural Network approach.[15] Except when the observed number of cases with the drug event combination is small

(e.g., less than 20) or the expected number of cases with the drug event combination is < 1 , the MGPS and PRR methods will generally identify similar drug event combinations for further investigation.[16]

Although all of these approaches are inherently exploratory or hypothesis generating, they may provide insights into the patterns of adverse events reported for a given product relative to other products in the same class or to all other products. FDA exercises caution when making such comparisons, because voluntary adverse event reporting systems such as AERS or VAERS are subject to a variety of reporting biases (e.g., some observations could reflect concomitant treatment, not the product itself, and other factors, including the disease being treated, other co-morbidities or unrecorded confounders, may cause the events to be reported). In addition, AERS or VAERS data may be affected by the submission of incomplete or duplicate reports, under-reporting, or reporting stimulated by publicity or litigation. As reporting biases may differ by product and change over time, and could change differently for different events, it is not possible to predict their impact on data mining scores.

Use of data mining techniques is not a required part of signal identification or evaluation. If data mining results are submitted to FDA, they should be presented in the larger appropriate clinical epidemiological context. This should include (1) a description of the database used, (2) a description of the data mining tool used (e.g., statistical algorithm, and the drugs, events and stratifications selected for the analyses) or an appropriate reference, and (3) a careful assessment of individual case reports and any other relevant safety information related to the particular drug-event combination of interest (e.g.,

results from preclinical, clinical, pharmacoepidemiologic, or other available studies).

F. Safety Signals That May Warrant Further Investigation

FDA believes that the methods described above will permit a sponsor to identify and preliminarily characterize a safety signal. The actual risk to patients cannot be known from these data because it is not possible to characterize all events definitively and because there is invariably under-reporting of some extent and incomplete information about duration of therapy, numbers treated, etc. Safety signals that may warrant further investigation may include, but are not limited to, the following:

1. New unlabeled adverse events, especially if serious;
2. An apparent increase in the severity of a labeled event;
3. Occurrence of serious events thought to be extremely rare in the general population;
4. New product-product, product-device, product-food, or product-dietary supplement interactions;
5. Identification of a previously unrecognized at-risk population (e.g., populations with specific racial or genetic predispositions or co-morbidities);
6. Confusion about a product's name, labeling, packaging, or use;

7. Concerns arising from the way a product is used (e.g., adverse events seen at higher than labeled doses or in populations not recommended for treatment);

8. Concerns arising from potential inadequacies of a currently implemented risk minimization action plan (e.g., reports of serious adverse events that appear to reflect failure of a RiskMAP goal);[17] and

9. Other concerns identified by the sponsor or FDA.

G. Putting the Signal into Context: Calculating Reporting Rates vs. Incidence Rates

If a sponsor determines that a concern about an excess of adverse events or safety signal warrants further investigation and analysis, it is important to put the signal into context. For this reason, calculations of the rate at which new cases of adverse events occur in the product-exposed population (i.e., the incidence rate) are the hallmark of pharmacoepidemiologic risk assessment. In pharmacoepidemiologic studies (see section V.A), the numerator (number of new cases) and denominator (number of exposed patients and time of exposure or, if known, time at risk) may be readily ascertainable. In contrast, for spontaneously reported events, it is not possible to identify all cases because of under-reporting, and the size of the population at risk is at best an estimate. Limitations in national denominator estimates arise because:

1. Accurate national estimates of the number of patients exposed to a medical product and their duration of exposure may not be available;

2. It may be difficult to exclude patients who are not at risk for an event, for example, because their exposure is too brief or their dose is too low;[18] and

3. A product may be used in different populations for different indications, but use estimates are not available for the specific population of interest.

Although we recognize these limitations, we recommend that sponsors calculate crude adverse event reporting rates as a valuable step in the investigation and assessment of adverse events. FDA suggests that sponsors calculate reporting rates by using the total number of spontaneously reported cases in the United States in the numerator and estimates of national patient exposure to product in the denominator.[19],[20] FDA recommends that whenever possible, the number of patients or person time exposed to the product nationwide be the estimated denominator for a reporting rate. FDA suggests that other surrogates for exposure, such as numbers of prescriptions or kilograms of product sold, only be used when patient-level estimates are unavailable. FDA recommends that sponsors submit a detailed explanation of the rationale for selection of a denominator and a method of estimation.

Comparisons of reporting rates and their temporal trends can be valuable, particularly across similar products or across different product classes prescribed for the same indication. However, such comparisons are subject to substantial limitations in interpretation because of the inherent uncertainties in the numerator and denominator used. As a result, FDA suggests that a comparison of two or more reporting rates be viewed with extreme caution and generally considered exploratory or hypothesis-generating. Reporting rates can by no means be

considered incidence rates, for either absolute or comparative purposes.

To provide further context for incidence rates or reporting rates, it is helpful to have an estimate of the background rate of occurrence for the event being evaluated in the general population or, ideally, in a subpopulation with characteristics similar to that of the exposed population (e.g., premenopausal women, diabetics). These background rates can be derived from: (1) national health statistics, (2) published medical literature, or (3) ad hoc studies, particularly of subpopulations, using large automated databases or ongoing epidemiologic investigations with primary data collection. FDA suggests that comparisons of incidence rates or reporting rates to background rate estimates take into account potential differences in the data sources, diagnostic criteria, and duration of time at risk.

While the extent of under-reporting is unknown, it is usually assumed to be substantial and may vary according to the type of product, seriousness of the event, population using the product, and other factors. As a result, a reporting rate higher than the background rate may, in some cases, be a strong indicator that the true incidence rate is sufficiently high to be of concern. However, many other factors affect the reporting of product-related adverse events (e.g., publicity, newness of product to the market) and these factors should be considered when interpreting a high reporting rate. Also, because of under-reporting, the fact that a reporting rate is less than the background rate does not necessarily show that the product is not associated with an increased risk of an adverse event.

V. BEYOND CASE REVIEW: INVESTIGATING A SIGNAL THROUGH OBSERVATIONAL STUDIES

FDA recognizes that there are a variety of methods for investigating a safety signal. Signals warranting additional investigation can be further evaluated through carefully designed non-randomized observational studies of the product's use in the "real world" and randomized trials. The Premarketing Guidance discusses a number of types of randomized trials, including the large simple safety study, which is a risk assessment method that could be used either pre- or post-approval.

This document focuses on three types of non-randomized observational studies: (1) pharmacoepidemiologic studies, (2) registries, and (3) surveys. By focusing this guidance on certain risk assessment methods, we do not intend to advocate the use of these approaches over others. FDA encourages sponsors to consider all methods to evaluate a particular safety signal. FDA recommends that sponsors choose the method best suited to the particular signal and research question of interest. Sponsors planning to evaluate a safety signal are encouraged to communicate with FDA as their plans progress.

A. Pharmacoepidemiologic Studies

Pharmacoepidemiologic studies can be of various designs, including cohort (prospective or retrospective), case-control, nested case-control, case-cross-over, or other models.[21] The results of such studies may be used to characterize one or more safety signals associated with a product, or may examine the natural history of a disease or drug utilization

patterns. Unlike a case series, a pharmacoepidemiologic study which is designed to assess the risk attributed to a drug exposure has a protocol and control group and tests prespecified hypotheses. Pharmacoepidemiologic studies can allow for the estimation of the relative risk of an outcome associated with a product, and some (e.g., cohort studies) can also provide estimates of risk (incidence rate) for an adverse event. Sponsors can initiate pharmacoepidemiologic studies at any time. They are sometimes started at the time of initial marketing, based on questions that remain after review of the premarketing data. More often, however, they are initiated when a safety signal has been identified after approval. Finally, there may also be occasions when a pharmacoepidemiologic study is initiated prior to marketing (e.g., to study the natural history of disease or patterns of product use, or to estimate background rates for adverse events).

For uncommon or delayed adverse events, pharmacoepidemiologic studies may be the only practical choice for evaluation, even though they can be limited by low statistical power. Clinical trials are impractical in almost all cases when the event rates of concern are less common than 1:2000-3000 (an exception may be larger trials conducted for some vaccines, which could move the threshold to 1:10,000). It may also be difficult to use clinical trials: (1) to evaluate a safety signal associated with chronic exposure to a product, exposure in populations with co-morbid conditions, or taking multiple concomitant medications, or (2) to identify certain risk factors for a particular adverse event. On the other hand, for evaluation of more common events, which are seen relatively often in untreated patients, clinical trials may be preferable to observational studies.

Because pharmacoepidemiologic studies are observational in nature, they may be subject to confounding, effect modification, and other bias, which may make results of these types of studies more difficult to interpret than the results of clinical trials. Some of these problems can be surmounted when the relative risk to exposed patients is high.

Because different products pose different benefit-risk considerations (e.g., seriousness of the disease being treated, nature and frequency of the safety signal under evaluation), it is impossible to delineate a universal set of criteria for the point at which a pharmacoepidemiologic study should be initiated, and the decision should be made on a case-by-case basis. When an important adverse event-product association leads to questions on the product's benefit-risk balance, FDA recommends that sponsors consider whether the particular signal should be addressed with one or more pharmacoepidemiologic studies. If a sponsor determines that a pharmacoepidemiologic study is the best method for evaluating a particular signal, the design and size of the proposed study would depend on the objectives of the study and the expected frequency of the events of interest.

When performing a pharmacoepidemiologic study, FDA suggests that investigators seek to minimize bias and to account for possible confounding. Confounding by indication is one example of an important concern in performing a pharmacoepidemiologic study.[22] Because of the effects of bias, confounding, or effect modification, pharmacoepidemiologic studies evaluating the same hypothesis may provide different or even conflicting results. It is almost always prudent to conduct more than one study, in more than one environment and even use

different designs. Agreement of the results from more than one study helps to provide reassurance that the observed results are robust.

There are a number of references describing methodologies for pharmacoepidemiologic studies, discussing their strengths and limitations,[23] and providing guidelines to facilitate the conduct, interpretation, and documentation of such studies.[24] Consequently, this guidance document does not comprehensively address these topics. However, a protocol for a pharmacoepidemiologic study generally includes:

1. Clearly specified study objectives;
2. A critical review of the literature; and
3. A detailed description of the research methods, including:
 - the population to be studied;
 - the case definitions to be used;
 - the data sources to be used (including a rationale for data sources if from outside the U.S.);
 - the projected study size and statistical power calculations; and
 - the methods for data collection, management, and analysis.

Depending on the type of pharmacoepidemiologic study planned, there are a variety of data sources that may be used, ranging from the prospective collection of data to the use of existing data, such

as data from previously conducted clinical trials or large databases. In recent years, a number of pharmacoepidemiologic studies have been conducted in automated claims databases (e.g., HMO, Medicaid) that allow retrieval of records on product exposure and patient outcomes. In addition, recently, comprehensive electronic medical record databases have also been used for studying drug safety issues. Depending on study objectives, factors that may affect the choice of databases include the following:

1. Demographic characteristics of patients enrolled in the health plans (e.g., age, geographic location);
2. Turnover rate of patients in the health plans;
3. Plan coverage of the medications of interest;
4. Size and characteristics of the exposed population available for study;
5. Availability of the outcomes of interest;
6. Ability to identify conditions of interest using standard medical coding systems (e.g., International Classification of Diseases (ICD-9)), procedure codes or prescriptions that could be used as markers;
7. Access to medical records; and
8. Access to patients for data not captured electronically.

For most pharmacoepidemiologic studies, FDA recommends that sponsors validate diagnostic findings through a detailed review of at least a sample of medical records. If the validation of the specific

outcome or exposure of interest using the proposed database has been previously reported, FDA recommends that the literature supporting the validity of the proposed study be submitted for review.

FDA encourages sponsors to communicate with the Agency when pharmacoepidemiologic studies are being developed.

B. Registries

The term registry as used in pharmacovigilance and pharmacoepidemiology can have varied meanings. In this guidance document, a registry is “an organized system for the collection, storage, retrieval, analysis, and dissemination of information on individual persons exposed to a specific medical intervention who have either a particular disease, a condition (e.g., a risk factor) that predisposes [them] to the occurrence of a health-related event, or prior exposure to substances (or circumstances) known or suspected to cause adverse health effects.”[25] Whenever possible, a control or comparison group should be included, (i.e., individuals with a disease or risk factor who are not treated or are exposed to medical interventions other than the intervention of interest).[26]

Through the creation of registries, a sponsor can evaluate safety signals identified from spontaneous case reports, literature reports, or other sources, and evaluate factors that affect the risk of adverse outcomes, such as dose, timing of exposure, or patient characteristics.[27] Registries can be particularly useful for:

1. Collecting outcome information not available in large automated databases; and

2. Collecting information from multiple sources (e.g., physician records, hospital summaries, pathology reports, vital statistics), particularly when patients receive care from multiple providers over time.

A sponsor can initiate a registry at any time. It may be appropriate to initiate the registry at or before initial marketing, when a new indication is approved, or when there is a need to evaluate safety signals identified from spontaneous case reports. In deciding whether to establish a registry, FDA recommends that a sponsor consider the following factors:

1. The types of additional risk information desired;
2. The attainability of that information through other methods; and
3. The feasibility of establishing the registry. Sponsors electing to initiate a registry should develop written protocols that provide: (1) objectives for the registry, (2) a review of the literature, and (3) a summary of relevant animal and human data. FDA suggests that protocols also contain detailed descriptions of: (1) plans for systematic patient recruitment and follow-up, (2) methods for data collection, management, and analysis, and (3) conditions under which the registry will be terminated. A registry-based monitoring system should include carefully designed data collection forms to ensure data quality, integrity, and validation of registry findings against a sample of medical records or through interviews with health care providers. FDA recommends that the size of the registry and the period during which data will be collected be consistent with the safety questions under study and we encourage sponsors to discuss their registry development plans with FDA.

C. Surveys

Patient or health care provider surveys can gather information to assess, for example:

1. A safety signal;
2. Knowledge about labeled adverse events;
3. Use of a product as labeled, particularly when the indicated use is for a restricted population or numerous contraindications exist;
4. Compliance with the elements of a RiskMAP (e.g., whether or not a Medication Guide was provided at the time of product dispensing); and [28]
5. Confusion in the practicing community over sound-alike or look-alike trade (or proprietary) names.

Like a registry, a survey can be initiated by a sponsor at any time. It can be conducted at the time of initial marketing (i.e., to fulfill a postmarketing commitment) or when there is a desire to evaluate safety signals identified from spontaneous case reports.

FDA suggests that sponsors electing to initiate a survey develop a written protocol that provides objectives for the survey and a detailed description of the research methods, including: (1) patient or provider recruitment and follow-up, (2) projected sample size, and (3) methods for data collection, management, and analysis.[29] FDA recommends that a survey-based monitoring system include carefully designed survey instruments and validation of survey findings against a sample of medical or pharmacy records or through interviews with

health care providers, whenever possible. FDA recommends that survey instruments be validated or piloted before implementation. FDA suggests that sponsors consider whether survey translation and cultural validation would be important.

Sponsors are encouraged to discuss their survey development plans with FDA.

VI. INTERPRETING SAFETY SIGNALS: FROM SIGNAL TO POTENTIAL SAFETY RISK

After identifying a safety signal, FDA recommends that a sponsor conduct a careful case level review and summarize the resulting case series descriptively. To help further characterize a safety signal, a sponsor can also: (1) employ data mining techniques, and (2) calculate reporting rates for comparison to background rates. Based on these findings and other available data (e.g., from preclinical or other sources), FDA suggests that a sponsor consider further study (e.g., observational studies) to establish whether or not a potential safety risk exists.

When evaluation of a safety signal suggests that it may represent a potential safety risk, FDA recommends that a sponsor submit a synthesis of all available safety information and analyses performed, ranging from preclinical findings to current observations. This submission should include the following:

1. Spontaneously reported and published case reports, with denominator or exposure information to aid interpretation;

2. Background rate for the event in general and specific patient populations, if available;
3. Relative risks, odds ratios, or other measures of association derived from pharmacoepidemiologic studies;
4. Biologic effects observed in preclinical studies and pharmacokinetic or pharmacodynamic effects;
5. Safety findings from controlled clinical trials; and
6. General marketing experience with similar products in the class.

After the available safety information is presented and interpreted, it may be possible to assess the degree of causality between use of a product and an adverse event. FDA suggests that the sponsor's submission provide an assessment of the benefit-risk balance of the product for the population of users as a whole and for identified at-risk patient populations, and, if appropriate, (1) propose steps to further investigate the signal through additional studies, and (2) propose risk minimization actions.[30] FDA will make its own assessment of the potential safety risk posed by the signal in question, taking into account the information provided by the sponsor and any additional relevant information known to FDA (e.g., information on other products in the same class) and will communicate its conclusions to the sponsor whenever possible. Factors that are typically considered include:

1. Strength of the association (e.g., relative risk of the adverse event associated with the product);
2. Temporal relationship of product use and the event;

3. Consistency of findings across available data sources;
4. Evidence of a dose-response for the effect;
5. Biologic plausibility;
6. Seriousness of the event relative to the disease being treated;
7. Potential to mitigate the risk in the population;
8. Feasibility of further study using observational or controlled clinical study designs; and
9. Degree of benefit the product provides, including availability of other therapies.

As noted in section II, risk management is an iterative process and steps to further investigate a potential safety risk, assess the product's benefit-risk balance, and implement risk minimization tools would best occur in a logical sequence, not simultaneously. Not all steps may be recommended, depending on the results of earlier steps.[31] FDA recommends that assessment of causality and of strategies to minimize product risk occur on an ongoing basis, taking into account the findings from newly completed studies.

VII. BEYOND ROUTINE PHARMACOVIGILANCE: DEVELOPING A PHARMACOVIGILANCE PLAN

For most products, routine pharmacovigilance (i.e., compliance with applicable postmarket requirements under the FDCA and FDA implementing regulations) is sufficient for postmarketing risk assess-

ment. However, in certain limited instances, unusual safety risks may become evident before approval or after a product is marketed that could suggest that consideration by the sponsor of a pharmacovigilance plan may be appropriate. A pharmacovigilance plan is a plan developed by a sponsor that is focused on detecting new safety risks and/or evaluating already identified safety risks. Specifically, a pharmacovigilance plan describes pharmacovigilance efforts above and beyond routine postmarketing spontaneous reporting, and is designed to enhance and expedite the sponsor's acquisition of safety information.[32] The development of pharmacovigilance plans may be useful at the time of product launch or when a safety risk is identified during product marketing. FDA recommends that a sponsor's decision to develop a pharmacovigilance plan be based on scientific and logistical factors, including the following:

1. The likelihood that the adverse event represents a potential safety risk;
2. The frequency with which the event occurs (e.g., incidence rate, reporting rate, or other measures available);
3. The severity of the event;
4. The nature of the population(s) at risk;
5. The range of patients for which the product is indicated (broad range or selected populations only); and
6. The method by which the product is dispensed (through pharmacies or performance linked systems only).[33]

A pharmacovigilance plan may be developed by itself or as part of a Risk Minimization Action Plan (RiskMAP), as described in the RiskMAP Guidance. Sponsors may meet with representatives from the appropriate Office of New Drugs review division and the Office of Drug Safety in CDER, or the appropriate Product Office and the Division of Epidemiology, Office of Biostatistics and Epidemiology in CBER regarding the specifics of a given product's pharmacovigilance plan.

FDA believes that for a product without safety risks identified pre- or post-approval and for which at-risk populations are thought to have been adequately studied, routine spontaneous reporting will be sufficient for postmarketing surveillance. On the other hand, pharmacovigilance plans may be appropriate for products for which: (1) serious safety risks have been identified pre- or post-approval, or (2) at-risk populations have not been adequately studied. Sponsors may discuss with the Agency the nature of the safety concerns posed by such a product and the determination whether a pharmacovigilance plan is appropriate.

A pharmacovigilance plan could include one or more of the following elements:

1. Submission of specific serious adverse event reports in an expedited manner beyond routine required reporting (i.e., as 15-day reports);
2. Submission of adverse event report summaries at more frequent, prespecified intervals (e.g., quarterly rather than annually);
3. Active surveillance to identify adverse events that may or may not be reported through passive surveillance. Active surveillance can be (1) drug based:

identifying adverse events in patients taking certain products, (2) setting based: identifying adverse events in certain health care settings where they are likely to present for treatment (e.g., emergency departments, etc.), or (3) event based: identifying adverse events that are likely to be associated with medical products (e.g., acute liver failure);

4. Additional pharmacoepidemiologic studies (for example, in automated claims databases or other databases) using cohort, case-control, or other appropriate study designs (see section V);

5. Creation of registries or implementation of patient or health care provider surveys (see section V); and

6. Additional controlled clinical trials.[34]

As data emerges, FDA recommends that a sponsor re-evaluate the safety risk and the effectiveness of its pharmacovigilance plan. Such re-evaluation may result in revisions to the pharmacovigilance plan for a product. In some circumstances, FDA may decide to bring questions on potential safety risks and pharmacovigilance plans before its Drug Safety and Risk Management Advisory Committee or the FDA Advisory Committee dealing with the specific product in question. Such committees may be convened when FDA seeks: (1) general advice on the design of pharmacoepidemiologic studies, (2) comment on specific pharmacoepidemiology studies developed by sponsors or FDA for a specific product and safety question, or (3) advice on the interpretation of early signals from a case series and on the need for further investigation in pharmacoepidemiologic studies. While additional information is being developed, sponsors working with FDA can take interim actions to communicate information about potential safety risks (e.g., through labeling) to minimize the risk to users of the product.

Notes

[1] This guidance has been prepared by the PD-UFA III Pharmacovigilance 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.

[2] For ease of reference, this guidance uses the term product or drug to refer to all products (excluding blood and blood components) regulated by CDER and 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).

[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>.

[4] Good reporting practices are extensively addressed in a proposed FDA regulation and guidance documents. See (1) Safety Reporting Requirements for Human Drug and Biological Products, Proposed Rule, 68 FR 12406 (March 14, 2003), (2) FDA guidance for industry on Postmarketing Reporting of Adverse Experiences, (3) FDA guidance for industry on E2C Clinical Safety Data Management: Periodic Safety Update Report (PSUR), (4) FDA guidance for industry on Postmarketing Adverse Experience Reporting for Human Drug and Licensed Biological Products: Clarification of What to Report.

[5] Patient outcomes may not be available at the time of initial reporting. In these cases, follow-up reports can convey important information about the course of the event and serious outcomes, such as hospitalization or death.

[6] See <http://www.nccmerp.org> for the definition of a medication error and taxonomy of medication errors.

[7] See, for example, Institute of Medicine (IOM) Immunization Safety Review on Vaccines and Autism, 2004.

[8] See World Health Organization, the Uppsala Monitoring Center, 2000, Safety Monitoring of Medicinal Product, for additional categorizations of causality.

[9] See Cohen MR (ed), 1999, Medication Errors, American Pharmaceutical Association, Washington DC; Cousins DD (ed), 1998, Medication Use: A Systems Approach to Reducing Errors, Joint Commission on Accreditation of Healthcare Organizations, Oakbrook Terrace, IL.

[10] Evans SJ, 2000, Pharmacovigilance: A science or fielding emergencies? *Statistics in Medicine* 19(23):3199-209; Evans SJW, Waller PC, and Davis S, 2001, Use of proportional reporting ratios (PRRs) for signal generation from spontaneous adverse drug reaction reports, *Pharmacoepidemiology and Drug Safety* 10:483-6.

[11] DuMouchel W and Pregibon D, 2001, Empirical Bayes screening for multi-item associations, Seventh ACM SigKDD International Conference on Knowledge Discovery and Data Mining.

[12] Szarfman A, Machado SG, and O'Neill RT, 2002, Use of screening algorithms and computer systems to efficiently signal higher-than-expected combinations of drugs and events in the US FDA's spontaneous reports database, *Drug Safety* 25(6): 381-92.

[13] Evans SJW, Waller P, and Davis S, 1998, Proportional reporting ratios: the uses of epidemiological methods for signal generation [abstract], *Pharmacoepidemiology and Drug Safety* 7:S102.

[14] Evans SJ, 2000, Pharmacovigilance: A science or fielding emergencies? *Statistics in Medicine* 19(23):3199-209; Evans SJW, Waller PC, and Davis S, 2001, Use of proportional reporting ratios (PRRs) for signal generation from spontaneous adverse drug reaction reports, *Pharmacoepidemiology and Drug Safety* 10:483-6.

[15] Bate A et al., 1998, A Bayesian neural network method for adverse drug reaction signal generation, *European Journal of Clinical Pharmacology* 54:315-21.

[16] This conclusion is based on the experience of FDA and of William DuMouchel, Ph.D., Chief Scientist, Lincoln Technologies, Wellsley, MA, as summarized in an email communication from Dr. DuMouchel to Ana Szarfman, M.D., Ph.D., Medical Officer, OPaSS, CDER, on October 13, 2004.

[17] For a detailed discussion of risk minimization action plan evaluation, please consult the RiskMAP Guidance.

[18] See Current Challenges in Pharmacovigilance: Pragmatic Approaches, Report of the Council for International Organizations of Medical Sciences (CIOMS) Working Group V, Geneva, 2001.

[19] See Rodriguez EM, Staffa JA, Graham DJ, 2001, The role of databases in drug postmarketing surveillance, *Pharmacoepidemiology and Drug Safety*, 10:407-10.

[20] In addition to U.S. reporting rates, sponsors can provide global reporting rates, when relevant.

[21] Guidelines for Good Pharmacoepidemiology, , International Society for Pharmacoepidemiology, 2004 http://www.pharmacoepi.org/resources/guidelines_08027.cfm

[22] See, for example, Strom BL (ed), 2000, *Pharmacoepidemiology*, 3rd edition, Chichester: John Wiley and Sons, Ltd; Hartzema AG, Porta M, and Tilson HH (eds), 1998, *Pharmacoepidemiology: An Introduction*, 3rd edition, Cincinnati, OH: Harvey Whitney Books.

[23] Ibid.

[24] Guidelines for Good Pharmacoepidemiology, International Society for Pharmacoepidemiology, 2004 http://www.pharmacoepi.org/resources/guidelines_08027.cfm

[25] See Frequently Asked Questions About Medical and Public Health Registries, The National Committee on Vital and Health Statistics, at <http://www.ncvhs.hhs.gov>

[26] See for example, FDA Guidance for Industry, Establishing Pregnancy Exposure Registries, August 2002 <http://www.fda.gov/cder/guidance/3626fnl.pdf>

[27] Ibid.

[28] For a detailed discussion of RiskMAP evaluation, please consult the RiskMAP Guidance.

[29] See 21 CFR parts 50 and 56 for FDA's regulations governing the protection of human subjects.

[30] In the vast majority of cases, risk communication that incorporates appropriate language into the product's labeling will be adequate for risk minimization. In rare instances, however, a sponsor may consider implementing a RiskMAP. Please refer to the RiskMAP Guidance for a complete discussion of RiskMAP development.

[31] For additional discussion of the relationship between risk assessment and risk minimization, please consult the RiskMAP Guidance.

[32] As used in this document, the term "pharmacovigilance plan" is defined differently than in the ICH draft E2E document (version 4.1). As used in the ICH document, a "pharmacovigilance plan" would be routinely developed (i.e., even when a

sponsor does not anticipate that enhanced pharmacovigilance efforts are necessary). In contrast, as discussed above, FDA is only recommending that pharmacovigilance plans be developed when warranted by unusual safety risks. This ICH guidance is available on the Internet at <http://www.fda.gov/cder/guidance/index.htm> under the topic ICH Efficacy. The draft E2E guidance was made available on March 30, 2004 (69 FR 16579). ICH agreed on the final version of the E2E guidance in November, 2004.

[33] For a detailed discussion of controlled access systems, please consult the RiskMAP Guidance.

[34] For a discussion of risk assessment in controlled clinical trials, please consult the Premarketing Guidance.

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Dr. Gerald Faich heads the UBC Epidemiology and Risk Management Group and is a recognized leader in drug safety and pharmacoepidemiology. His research interests are risk assessment, pharmacoepidemiology and the design and conduct of registries and streamlined trials for phase IIIb and IV. Before joining UBC, Dr. Faich served in senior management positions at FDA and Corning and provided high-level consulting on safety and risk issues. He is currently a visiting scholar at the University of Pennsylvania and President of the International Society for Pharmacoepidemiology.

Dr. Faich received his undergraduate and medical degrees with honors from the University of Wisconsin. An Internal Medicine residency and Masters degree in Public Health at Harvard followed this. He is a Fellow of the American Colleges of Physicians, Preventive Medicine and Pharmacoepidemiology and has authored over 90 scientific papers and received numerous awards, including FDA's Outstanding Service Award for contributions to Postmarketing Surveillance and Public Health.

From 1983 to 1990, Dr. Faich was the Office Director in charge of statistics and postmarketing surveillance for drugs and biologics at the FDA. There he revitalized the adverse reaction reporting system, revised reporting regulations, expanded staffing and pharmacoepidemiologic research. He co-chaired the original CIOMS International Adverse Reaction Working Group and was a founding board member of the International Society for Pharmacoepidemiology.

After leaving FDA Dr. Faich served as President of PACT, a CRO which focused on postmarketing research and Corning Pharmaceutical Services (now Covance) where he had overall responsibility for toxicology, laboratory testing and phase I to IV clinical trial units. He formed a consulting company in 1996 and joined UBC in 2004.

Annette Stemhagen, DrPH, FISPE
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Dr. Annette Stemhagen has more than 25 years of public health epidemiological research experience, including 15 years in safety surveillance of pharmaceutical, biotech and vaccine products. She is the Vice President of Epidemiology and Risk Management within United BioSource Late Stage Group, where she provides strategic consultative services to pharmaceutical and biotech clients in epidemiology, safety surveillance, and risk management and assists other UBC groups in developing and implementing creative and innovative study design solutions to meet client needs. Dr. Stemhagen has specific expertise in design, implementation, and analysis of epidemiologic studies, registries, large streamlined safety studies and actual use and observational studies for products in Phase IIIb and post approval. She has designed and evaluated risk assessment studies, including more than 10 regulatory-mandated long term safety studies. She has also developed risk intervention programs, risk management evaluation studies, and Risk MAPS. Dr. Stemhagen is active in the International Society for Pharmacoepidemiology and the Drug Information Association. In 2004, Dr. Stemhagen was appointed as the industry representative to the FDA Drug Safety and Risk Management Advisory Committee.

Dr. Stemhagen received her undergraduate degree from the University of Pennsylvania, and her Masters and Doctoral Degrees from the University of Pittsburgh Graduate School of Public Health in epidemiology. She holds adjunct faculty appointments at the University of Pennsylvania School of Medicine Center for Epidemiology and Biostatistics and the Temple University School of Pharmacy. Dr. Stemhagen is a Fellow of the International Society for Pharmacoepidemiology.

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