Guidance for Industry

Premarketing Risk Assessment

DRAFT GUIDANCE

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

May 2004
Clinical Medical

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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 are being developed on 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.

[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. Similarly, for ease of reference, this draft guidance uses the term *approval* to refer to both drug approval and biologic licensure.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).

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 producing three draft guidance documents on risk management activities:

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 that preceded them, each of the three draft guidance documents focuses on one aspect of risk management.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

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

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

  Industry already performs risk assessment and risk minimization activities for products during development and marketing. The Federal Food, Drug, and Cosmetic Act (FDCA) and FDA implementing regulations establish requirements for ***routine*** risk assessment and risk minimization (e.g., FDCA sec. 503(b) (21 U.S.C. 353(b)), which provides for

limiting drugs to prescription status, FDA regulations regarding spontaneous adverse event reporting and FDA-approved professional labeling). As a result, many of the recommendations presented here focus on situations when a product may pose an unusual type or level of risk. To the extent possible, we have specified in the text whether a recommendation is intended to apply to all products or only this subset of products.

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

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

- To the extent possible, this guidance conforms with FDA's commitment to harmonize international definitions and standards as 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 stakeholder input (e.g., from consumers, pharmacists, physicians, third party payers).

- There are points of overlap among the three guidances.

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

III. THE ROLE OF RISK 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 product as a candidate, through the premarketing development process, and after marketing. Premarketing risk

[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.

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. For the underlying risks, sponsors should provide a body of evidence from the clinical trials that adequately characterizes the product's safety profile.[4]

This guidance provides general recommendations for assessing risk. The adequacy of this assessment is a matter of both quantity (ensuring that enough patients are studied) and quality (the appropriateness of the assessments performed 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.

[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*, endorsed by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and published in the *Federal Register* on March 1, 1995 (60 FR 11270).

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 sponsors pay careful attention from the outset of development 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. Some risks become apparent only when a product is used in tens of thousands or even millions of patients in the general population. However, the larger and more comprehensive a preapproval database, the more likely it is that serious adverse events will be detected.

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 potential advantages of the product over existing therapy
- The intended population
- The intended duration of use

Safety databases for products intended to treat life-threatening diseases are usually smaller than for products supporting symptomatic treatment of nonserious disease. 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.

For products intended for short-term or acute use, 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. Products intended for life-threatening and severely debilitating diseases are often approved with relatively small safety databases and, thus, relatively greater uncertainty regarding their adverse effects. Section 312.82(b) (21 CFR 312.82(b)) provides that end-of-phase 1 meetings will 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."[6]

[6] Subpart E of 21 CFR part 312 addresses investigational new drug (IND) applications for drugs intended to treat life-threatening and severely debilitating illnesses.

For products intended for long-term treatment (e.g., chronic or recurrent intermittent) of non-life-threatening conditions, 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).[7] 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 patients exposed for 1 year should have been exposed to relevant doses, with a reasonable representation of subjects exposed at the highest proposed dose.

We note that it is common for well-conducted clinical development programs to explore doses higher than those ultimately proposed for marketing. In such cases, data from patients exposed to doses in excess of those ultimately proposed are informative 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)

[7] 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.*

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.

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. A safe and effective alternative to the investigational product is already available.

The 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 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 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 patient 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.

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) are of significance and interpretable whenever they occur since the expected rate is essentially zero in populations of any feasible size. They thus can usually be appropriately interpreted without 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 are conducted 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 its earlier clinical and preclinical safety assessments. (See section D below for further discussion of comparative trials.)

2. A Diverse Safety Database

Premarketing safety databases should include, to the extent possible, a diverse population in phase 3 studies. FDA has previously addressed this issue in a memorandum,[8] and the recommendations provided here are intended to supplement that document. We recommend that, to the extent feasible, only patients with obvious contraindications be excluded from study entry in phase 3 trials. Inclusion of a diverse population allows for the development of safety data in a broader population that includes patients previously excluded from clinical trials, such as the elderly (particularly the very old), patients with concomitant diseases, and patients taking usual concomitant medications. Broadening inclusion criteria in phase 3 studies enhances the generalizability of study findings and may, therefore, allow the product to be labeled for broader use. Although some phase 3 efficacy studies may target certain demographic or disease characteristics (and hence have narrower inclusion and exclusion criteria), it may be useful to conduct controlled safety and/or efficacy studies in 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 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:

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[8] 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 Web page under FDAMA guidances (http://www.fda.gov/cder/guidance/women.pdf).

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

In circumstances when phase 2 studies cannot reasonably be considered to have established a single most appropriate dose, more than one dose level should usually be used in phase 3 trials to better characterize the relationship between product exposure and resulting clinical benefit and risk. In such cases, dose-response data from phase 3 trials with multiple dose levels help to better define the relationship of exposure to dose for both safety and effectiveness. Inadequate exploration of a product's dose-response relationship in clinical trials raises safety concerns, since recommending doses in labeling that exceed the amount needed for effectiveness may increase risk to patients 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.[9]

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 address a number of potential 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

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

- 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

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 incorporating pharmacokinetic (PK) assessments (e.g., population PK studies) into a subset of clinical trials, including safety trials. PK assessments could aid in the detection of unexpected PK interactions and, in some cases, with careful analysis, could suggest exposure-response relationships for both safety and efficacy. Such data would allow for better assessment of whether PKs contribute to any adverse events seen in the clinical trials, particularly rare, serious, and unanticipated events.

When a product has one or more 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. Use of a placebo would also help to show whether either drug actually caused the adverse events.

- There is a well-established related therapy.

  A comparative 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.

- 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.

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. [10]

A. Risk Assessment During Product Development

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

- 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 may be appropriate.

  For example, for drugs with likely CNS effects, sponsors should conduct an assessment of cognitive function, motor skills, sexual function, and mood. The use of targeted safety questionnaires or specific psychometric or other validated instruments is often important

[10] 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 should principally be initiated after marketing, the *Pharmacovigilance Guidance* discusses certain situations when they could be initiated preapproval.

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).

- Particularly in circumstances when earlier safety data signal an unusual or important concern, a sponsor should consider reserving blood samples (or any other bodily fluids/tissues that may be collected during clinical trials) from some or all patients in phase 3 studies for possible assessments at a later time. Such later assessments could include pharmacogenomic markers, 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 some 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, e.g., to assess the rate of rare events. An LSSS is most commonly performed postapproval either as a phase 4 commitment or outside of a formal phase 4 commitment in response to a new safety concern. Circumstances in which an LSSS may be appropriate prior to approval include the following.

- When 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 needed if the safety signal cannot otherwise be better delineated or refuted.

- When there are early signals (i.e., preclinical or clinical) of serious toxicities or other unique or special considerations (e.g., regarding the safety of the use of the product with a concomitant medication where the previous clinical data have not addressed the issue sufficiently). In such cases, LSSS data could help better characterize the risk.[11]

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

[11] 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.

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. Risk Assessment and Minimizing the Potential for Medication Errors

Sponsors can help minimize the risk of medication errors involving their products by conducting a premarketing risk assessment to document that a product's proprietary name, established name, container label, carton labeling, patient/consumer labeling, professional package insert labeling, and packaging do not inadvertently contribute to medication errors. For purposes of this guidance, this premarketing risk assessment is referred to as a medication error prevention analysis (MEPA). A well-planned and conducted MEPA would do the following:

- Identify known and potential medication errors
- Identify reasons or potential causes for each identified error (e.g., dosage form, packaging, labeling, or confusion due to trade names when written or spoken)
- Place each identified error into the context of its resultant risk, according to expected or potential outcomes
- Minimize the potential for medication errors through premarketing risk minimization actions, including proper naming, labeling, design, and packaging

FDA currently undertakes some of the activities discussed in this section. However, sponsors may be able to help reduce medication errors if they engage in premarketing risk assessments to support their proposed names, labeling, and packaging.

MEPAs can employ a number of techniques to assess for potential medication errors, including Failure Mode and Effects Analysis (FMEA), expert panels, computer assisted analysis, direct observation, clinical trials, directed interviews of consumers, medical and pharmacy personnel, focus groups, and simulated prescription and over the counter (OTC) use studies. Sponsors should use multiple techniques when performing MEPA assessments. The most appropriate mix of techniques for any particular product will depend on the issues being assessed.

FDA recognizes the skill and experience of the U.S. Adopted Names Council (USAN), on which the Agency has representation, in deriving established names for drug products (see 21 CFR 299.4). USAN negotiates with manufacturing firms in the selection of names for drugs. The FDA is authorized, however, under section 508 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 358) to designate an official name for any drug if it determines that such action is necessary or desirable in the interest of usefulness or simplicity (see 21 CFR 299.4(a)). To facilitate such determinations and due to the documented number of errors associated with established names that have led to patient injury, we recommend that sponsors perform MEPAs on established names they propose for products. We recommend that sponsors use the risk assessment techniques described above, as appropriate, before submitting such names to the USAN Council and FDA.

The Agency cannot fully address MEPAs in this guidance. A specific and expanded guidance on medication error prevention analysis is being developed. Currently, sponsors planning to initiate a MEPA may seek guidance on study design from the Division of Medication Errors and Technical Support in the Office of Drug Safety when submitting a drug application to a new drug review division, or from the Office of Compliance and Biologics Quality when submitting an application to a CBER product office.

C. Safety Aspects that Should Be Addressed During Product Development

The potential for the following serious adverse effects should be addressed as a part of all new small molecule drug development programs.

- 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 when these effects occur, they are often definable in clinical development programs (when properly assessed) and have important safety ramifications for products. Although FDA believes these potential effects should be addressed in all drug programs, addressing them would not always involve the generation of data. 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.

Many of these 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 guidance *E3 Structure and Content of Clinical Study Reports*. We do not repeat that guidance here, but offer new guidance on selected issues.

A. Describing Adverse Events to Identify Safety Signals

Because individual investigators may use different terms to describe a particular adverse event, sponsors should 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 throughout a clinical program. 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.

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 adverse events are 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, should be well documented with an audit trail.

- In addition to ensuring that investigators have accurately characterized adverse events, we recommend that 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 preferred 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 liability*.

- 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. To examine the extent of variability in the coding process, FDA recommends that 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 preferred 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 cases. 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 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 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 are not detected 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 causality (e.g., an increasing rate of events over time could suggest causality). 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 (e.g., 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, 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 preclinical 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.

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 arbitrary in nature. It may be useful in such cases to make a specific effort to examine safety (and efficacy) just above and below the cut 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, distinguished in post hoc explorations of the data, 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. Data pooling can be used for comparative studies or for single-arm studies. 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 chance findings in individual studies. However, a finding should not be automatically dismissed, especially if it is detected in a study of superior design or in a different population.

Although false positive signals resulting from data pooling are concerning, a false negative signal may have larger public health implications. False negative signals may result from inappropriate pooling. Therefore, any pooled analyses 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 include, but are not limited to, differences in the duration of studies, heterogeneous 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).

A pooled analysis may be less informative when there is clinical heterogeneity with regard to the safety outcome of interest (e.g., major differences between trials). In these cases, sponsors should present risk information on the range of results in individual studies separately, rather than use a summary value from a pooled analysis.

E. Using Pooled Data During 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 is most likely to 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 drop outs.

  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 whenever a pooled analysis is planned.

F. Rigorous Ascertainment of Reasons for Withdrawals from Studies

Subjects may dropout 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 irrelevant (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 account for all dropouts and 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,” or “lost to follow-up.” Participants who leave a study because of serious or significant safety issues should be followed closely until they are fully and permanently resolved, with follow-up data recorded in the case report forms.

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.

H. Important Aspects of Data Presentation

Once a product's safety data have been analyzed, we recommend that comprehensive risk assessment information be presented succinctly. FDA and ICH have provided extensive guidance regarding the presentation of safety data,[12,13] and we offer these additional recommendations, which have not been formerly addressed.

- 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 common to the class 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. When establishing case definitions for particular adverse events, we recommend that sponsors consider definitions previously used for the other drugs in the class.

- 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

[12] See *Guideline for the Format and Content of the Clinical and Statistical Section of an Application*.
[13] See the guidance for industry *E3 Structure and Content of Clinical Study Reports*.

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 hospital records, autopsy reports, biopsy reports, and radiological reports, where applicable.

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

- Narrative summaries (as previously described in guidance[14]) 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.

  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
  – Outcomes and follow-up information

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