Guidance for Industry

Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment

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)

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Contains Nonbinding Recommendations

TABLE OF CONTENTS

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I. INTRODUCTION

This document provides guidance to industry on good pharmacovigilance practices and pharmacoepidemiologic assessment of observational data regarding drugs, including biological drug products (excluding blood and blood components).[2] Specifically, this document provides guidance on (1) safety signal identification, (2) pharmacoepidemiologic assessment and safety signal interpretation, and (3) pharmacovigilance plan development.

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

[1] This guidance has been prepared by the PDUFA 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.

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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.

[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.

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.

[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*.

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.

[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.

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] 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.

6. Existence of other supporting evidence from preclinical studies, clinical trials, and/or pharmacoepidemiologic 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 pharmacoepidemiologic 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;

[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.

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

[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.

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

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[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.

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.

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

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

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[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.

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-crossover, 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

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

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.

[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.

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;

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[23] Ibid.

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

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

[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.

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

[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.

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 assessment. 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

[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*.

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.

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[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*.

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.

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