Guidance

Classifying Significant Postmarketing Drug Safety Issues

DRAFT GUIDANCE

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Drug Safety

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Guidance[1]
Classifying Significant Postmarketing Drug Safety Issues

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I. INTRODUCTION

This guidance describes the framework the U.S. Food and Drug Administration's (FDA's) Center for Drug Evaluation and Research (CDER) intends to use in classifying significant postmarketing drug[2] safety issues as *priority*, *standard*, or *emergency*. Significant postmarketing safety issues include serious adverse events, product quality issues, and medication errors. This classification framework will enable CDER to direct its resources toward the safety issues that pose the greatest potential risk for patients. CDER invites public comment on the factors to be used and the methodological approach.

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

As explained in FDA's mission statement, it is FDA's responsibility to (1) *promote the public health* by promptly and efficiently reviewing clinical research and taking appropriate action on the marketing of regulated products in a timely manner, and (2) *protect the public health* by ensuring that human drugs are safe and effective. To fulfill those goals, before drugs can be marketed, CDER rigorously evaluates new drug applications (NDAs) and biologics license applications (BLAs) to ensure that the benefits of the drugs exceed the risks for their intended use.

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

[2] For purposes of this guidance the term *drug* includes drug and therapeutic biological products.

FDA monitors and reviews safety information about a drug throughout the product's lifecycle, interacting with sponsors during product development and clinical investigation of the drug, closely reviewing safety issues during consideration of a marketing application, and, if the drug is approved, monitoring safety reports after the drug is marketed. Every approved drug has labeling (e.g., prescribing information) that contains, among other things, information about the benefits and risks of using the drug. Because all drugs have risks, health care professionals and patients must balance the risks and benefits of a drug when making decisions about drug therapy.

After drug approval, FDA may learn of new, more serious, or more frequent adverse drug reactions from, for example, postapproval voluntary or mandatory reporting of adverse drug reactions during use of the drug; postapproval clinical trials exploring new uses of the drug; or other postapproval studies, including epidemiologic studies or active surveillance evaluations. For example, additional adverse drug reactions, some of them serious, may be identified once a drug is used more widely and under more diverse conditions (e.g., concurrent use with other drugs), or when the drug is prescribed for off-label uses. In some cases, medication errors can occur because of name confusion or other factors that influence safe use of the medication. CDER integrates what is learned from required sponsor reporting and its own evaluations into an overall system of postmarketing surveillance and risk assessment both to identify safety issues that were not identified during the clinical development program and to learn more about issues that may have occurred but were difficult to interpret. The Center uses this information to take appropriate action when the risks indicate a need to provide additional safety information to the public, to update drug labeling, to require postmarketing studies or trials, to require additional risk management interventions, or, on rare occasions, to remove a drug from the market.

The Prescription Drug User Fee Act of 1992 and its reauthorizations brought predictability and accountability to the new drug review process. By providing needed funds and supporting carefully managed timelines and review goals, PDUFA ended slow and unpredictable review of and action on NDAs and BLAs while maintaining FDA's high review standards. Recently, CDER has begun to apply a similar approach to managing postmarketing safety. This is in part a response to a number of studies of CDER's postmarketing activities that raised concerns about the predictability and timeliness of the Center's regulatory decision-making after postmarketing safety issues were identified.[3] CDER has undertaken a number of initiatives to strengthen the management of postmarketing safety evaluations and bring the same focus and accountability to postmarketing safety review as it established for premarket review of new drugs. This guidance reflects one step in that process: prioritization of identified safety issues according to an established set of criteria.

III. TRACKING SIGNIFICANT SAFETY ISSUES

In January 2007, CDER took an important step forward when it launched the Document Archiving, Reporting, and Regulatory Tracking System (DARRTS) module for centralized tracking of significant postmarketing safety issues. This system enables CDER to share information, including project plans, document reviews, and recommendations for regulatory action, across multiple offices.

[3] See http://www.fda.gov/Drugs/DrugSafety/ucm187806.htm.

CDER receives a constant flow of information about potential drug safety issues. The seriousness of reported problems varies widely. Those that are determined to be significant safety issues are tracked in DARRTS. To be considered significant, the problem or adverse event of concern must meet certain criteria. In general, CDER considers postmarketing safety issues to be significant for tracking purposes if they have the potential to lead to any of the following actions:

- Withdrawal of FDA approval of a drug
- Withdrawal of an approved indication
- Limitations on a use in a specific population or subpopulation
- Additions or modifications to the Warnings and Precautions, or Contraindications sections of the labeling, or the Medication Guide or other required Patient Package Insert, including safety labeling changes required under the Food and Drug Administration Amendments Act (FDAAA)
- Establishment of or changes to the proprietary name/container label/labeling/packaging to reduce the likelihood of medication errors
- Establishment or modification of a risk evaluation and mitigation strategy (REMS)
- A requirement that a sponsor conduct a safety-related postmarketing trial or study
- The conduct of a safety-related observational epidemiological study by FDA

When CDER staff consider a safety issue to be significant, according to the threshold criteria listed above, a DARRTS tracked safety issue (TSI) is opened. Typically, an interdisciplinary team assesses the safety issue, re-evaluates the risk–benefit profile of the drug, and determines the need for regulatory action.

A. The Next Step — A Framework for Prioritizing TSIs

Since the introduction of the DARRTS safety tracking function, almost 1,000 TSIs have been entered into the system. Although all of these issues are considered significant, all 1,000 TSIs are not, in fact, of the same urgency. Without sufficient resources to manage all TSIs equally, FDA has been prioritizing them on a case-by-case basis, but without an agreed-to priority framework.

The Center is now seeking to establish a formal framework for prioritizing TSIs so that CDER can direct resources more effectively toward those issues posing the greatest potential risk to patients. This framework will classify TSIs as *priority*, *standard*, or *emergency*. The use of a formal framework is intended to ensure that staff working in different offices across CDER have a common understanding of the relative urgency of TSIs and direct attention to those that need to be addressed most expeditiously. The framework will also inform CDER decisions about public

drug safety communications so that health care professionals and patients receive timely information about safety risks with the greatest public health significance.[4]

The proposed framework for classifying postmarketing safety issues will help ensure that resources are consistently focused on those issues with the greatest public health significance. Although all postmarketing safety issues will continue to be thoroughly investigated, those deemed to be *priority* or *emergency* will be most closely monitored, tracked, and managed with clear timelines for decision-making.

B. Prioritization — Part of an Evaluation Process

Identifying and prioritizing postmarketing safety signals are only the first steps in evaluating a suspected safety problem. Once identified, the analysis of the possible safety issue requires identifying all sources of pertinent data and analyzing them, weighing findings against the established benefits of the drug, and deciding on the appropriate steps for dealing with the identified problem. This guidance addresses only the factors to be used to prioritize a newly identified safety issue. The evaluation of the issue, weighing benefits and risks, and optimizing risk mitigation or risk management activities will not be addressed here, but are the subject of additional ongoing Agency work.

Once an issue has been prioritized, CDER staff will promptly develop and implement a plan to fully evaluate the risk and take appropriate actions. Initial activities may range from analysis of existing data to requests for more data from the drug's sponsor. Differences in evaluation needs will determine how soon regulatory action can be taken, but, especially for priority issues, there will be a prompt and continuous effort to ensure that the appropriate steps are taken expeditiously. Once CDER reaches a conclusion about the safety issue and decides to take action, the action may include, for example, requiring changes to the drug's labeling, requiring additional risk management interventions such as a risk evaluation and mitigation strategy (REMS), requesting voluntary withdrawal, or initiating proceedings to withdraw approval of the application resulting in removal of the product from the market.

CDER makes decisions about the appropriate regulatory action only after balancing the potential risks posed by the drug against the magnitude and nature of established clinical benefits, the uniqueness of those benefits (i.e., whether there are alternative treatments with similar benefits), and the severity of the disease or condition the drug is used to treat in the context of the populations the drug is intended to treat.

IV. METHODOLOGICAL FRAMEWORK

CDER will use *hazard assessment criteria* and will then apply certain *modulating factors* to classify a newly identified safety issue. CDER staff will first apply the criteria used to estimate

[4] A draft guidance *Drug Safety Information – FDA's Communication to the Public* is available at http://www.fda.gov/Drugs/Guidance ComplianceRegulatorInformation/Guidances/default.htm. It revises the guidance of the same name issued in 2007. When finalized, the draft guidance will reflect the agency's current thinking on this subject.

the hazard that the suspected safety problem poses to patients. This will yield a preliminary classification of either *priority* or *standard*. Staff will then examine the issue in relation to the context of the drug's use, biological plausibility, and other factors. Based on this examination, staff may modify the preliminary classification. When the safety issue does not appear to fall clearly into either the priority or standard class, CDER will err on the side of caution and classify it as a priority issue.

The Center may consider selected *priority* safety issues to be *emergencies*, particularly if they have involved fatalities, have the potential to affect a very large number of patients, and if lives can be saved or if serious harm can be prevented by prompt action. Emergency issues will be immediately elevated to the attention of senior management.

All tracked safety issues (TSIs) not classified as *priority* or *emergency* following this approach will be considered *standard*.

A. The Hazard Assessment

The criteria for determining whether a postmarketing safety issue is significant for tracking purposes are essentially surrogates for the seriousness of the issue. By and large, a TSI will meet the regulatory definition of a serious adverse drug experience (21 CFR 314.80(a)), and for any TSI, there will be credible evidence at the time the issue is initially tracked that the significant safety issue could be associated with the drug.

Once this threshold is met, CDER will estimate the hazard posed by a significant tracked safety issue, based on three variables: (1) the relative seriousness of the issue; (2) the estimated size of the population exposed to the risk of the drug; and (3) the suspected frequency of harm to patients exposed to the drug. The combination of factors 2 and 3 provides an estimate of population risk; the combination of factors 1 and 3 provides an estimate of personal risk to the patient.

1. Relative Seriousness of the Safety Issue

CDER will determine the relative seriousness of a safety issue as *high* or *medium*. In general, the seriousness will be considered to be high if the risk is fatal, life-threatening, or requires hospitalization. Examples of adverse medical events considered highly serious include, for example, acute myocardial infarction, stroke, acute renal failure, acute hepatic injury, progressive multifocal leukoencephalopathy, anaphylaxis, and toxic epidermal necrolysis. Most likely, a safety issue considered highly serious would be classified as a priority TSI. A serious safety issue that does not involve fatal or life-threatening risks would be considered to be of medium relative seriousness and would depend on a large exposure and/or high relative risk to be considered a priority TSI.

2. Estimated Size of the U.S. Population Exposed to Risk of the Drug

CDER will consider the rate of patient exposure to be high if over 1 million patients use the drug. A recent CDER analysis of almost 2,200 active ingredients sold through U.S.

retail pharmacies shows a nearly bimodal distribution of patient exposure.[5] A very small percentage (3%) were used by more than 5 million outpatients within the past year, and only 11% were used by more than 1 million. In contrast, 86% were used by fewer than 500,000 outpatients. This analysis did not include drugs distributed through inpatient care settings, such as hospitals, or address the length of patient exposure to the drugs. However, the numbers are sufficiently compelling to suggest that drugs with very high levels of patient exposure are uncommon. CDER reviewers will therefore rate the magnitude of patient exposure as *high* in a relatively small fraction of cases.

3. Suspected Frequency of Harm to Patients Exposed to Risk from the Drug

Available information regarding frequency of harm will be taken into account along with the context in which the drug is being used (see Modulating Factors). For example, if the risk of concern is a common event in the United States, such as stroke or myocardial infarction, a small increase in risk (e.g., 20%) could be a reason for elevating the status of the TSI to *priority* because even a small increase in risk could affect a large number of patients. In contrast, if the risk of concern is not common, a small increase in risk might not be a reason to elevate the status of a TSI to *priority*.

The estimate of harm will be refined as more data become available. In general, for the purpose of classification of a TSI, CDER staff will use a conservative approach to risk estimates — a *high end* estimate in the face of variable data. For example, frequency estimates will often include both a point estimate and a measure of variance. For the purpose of classification, when there is a reasonable amount of data, the upper bound of the confidence interval would be used to estimate risk.

When CDER staff identify a new safety issue, unless the information is derived from a clinical trial or pharmacoepidemiology study, precise and reliable information may be lacking about the frequency of the adverse event or the increase in risk posed to patients exposed to the drug. If such information is lacking, staff will use the existing information on seriousness, and size of the population at risk, and then the modulating factors to classify the TSI.

B. Modulating Factors

After assessing the hazard posed by the safety issue, based on the three factors discussed above, CDER staff may consider a range of other factors that have the potential to elevate or, in some circumstances, lower the classification of the safety issue. These factors tend to fall into three broad categories.

1. Context of the Drug's Use

Considerations arising from the context of use would include, but not be limited to, the following.

[5] CDER OSE analysis of data on outpatient use of drugs from SDI, Total Patient Tracker, September 2009 - August 2010, Extracted October 2010. The 2,200 active ingredients each had over 1,000 prescriptions dispensed within the last 12-month period and accounted for approximately 92% of all dispensed prescriptions in the outpatient setting.

- The availability and risk profiles of therapeutic alternatives

Whether the drug provides unique clinical benefits, or whether there are other drugs with the same indication that are considered relatively safe and thus offer robust alternatives to patients, will be considered as a modulating factor. A suspected serious safety issue for a drug with several safe alternatives would more likely be classified as *priority* than a safety issue for a drug providing unique benefits.

- Risks posed to vulnerable populations

CDER is mindful of risks posed to certain vulnerable populations, such as pediatric patients, older patients, and pregnant women. Evidence that a drug poses a risk to such populations would more likely weigh in favor of making the safety issue a *priority*.

- The clinical setting in which the drug is used

Occurrence of a serious risk in an unsupervised setting is likely to raise the level of CDER concern and make the safety issue a priority. For example, CDER would consider whether the safety issue occurs with an OTC medication whose use is widespread and medically unsupervised, or whether it is used in a hospital or other supervised care setting.

2. The Quality of the Data Suggesting the Risk

Spontaneous adverse event reports and published analyses differ greatly, for example, in their quality, the methodology used, the reported strength of the findings, and whether the findings are replicated. For published reports, the quantity of data presented may be highly variable and the underlying data may or may not be available for review. The overall credibility of a safety finding is an important modulating factor for determining its classification. The higher the credibility of the data, the more likely it will be considered a priority TSI.

3. Biologic Plausibility

CDER will consider whether there is a biologically plausible explanation for the association of the drug and the safety signal, based on what is known from systems biology and the drug's pharmacology. The more biologically plausible a risk is, the greater consideration will be made to classifying a safety issue as a priority.

V. NEXT STEPS

CDER invites public comment on the proposed approach and criteria to be used for classifying TSIs as *priority*, *standard*, or *emergency*. After analyzing the comments, the Center will

consider whether to modify its approach to classifying significant safety issues and will finalize this guidance.

Within the next year, CDER will begin implementing this framework to ensure that priority safety issues, including emergency safety issues, receive rapid attention. Unlike reviews of premarket applications, which typically contain all or most of the data needed for regulatory decision making, postmarketing safety reviews often begin when data are sparse or inadequate for regulatory decision making. For this reason, resolution of postmarketing safety issues does not lend itself to completion within fixed time frames. Despite this inherent difficulty, CDER will make operational changes to shorten the time needed to assess and act on priority safety issues. Roles and responsibilities will be clarified so that there is a clear path to decision making. After pilot testing this system, the Center intends to develop specific milestones for taking action on priority and standard TSIs, similar to those now used for premarket applications.

Under the new system, whenever a new priority safety issue is identified, review teams will develop work plans incorporating these milestones and the issues will be managed in accordance with the work plans.