Congratulations! Your company’s New Drug Application (NDA) was approved and your drug marketing plan is a huge success. Having successfully managed risk prior to approval and immediately thereafter, what steps should your company now take to assess and minimize safety risks? For many products, routine compliance with postmarket requirements set forth in the Federal Food, Drug, and Cosmetic Act (FDCA) and Food and Drug Administration implementing regulations is sufficient for postmarketing risk assessment. In some circumstances, however, unusual safety risks may suggest a need for a formal pharmacovigilance plan.

To help sponsors understand the importance of pharmacovigilance activities in the post-approval period, the United States Department of Health and Human Services, Food and Drug Administration, and Center for Drug Evaluation and Research (collectively referred to as “FDA”) published in March 2005 a Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment (Guidance). The Guidance applies to all drugs, except blood and blood components. While the recommendations set forth in the Guidance are nonbinding, they represent FDA’s current thinking on what must be done to assess and manage risk post-marketing. More specifically, the Guidance sets forth recommendations on (1) safety signal identification; (2) pharmacoepidemiologic assessment; and (3) pharmacovigilance plan development.

What is Pharmacovigilance?
Pharmacovigilance means “all scientific and data gathering activities relating to the detection, assessment, and understanding of adverse events.”

Identifying and Reporting Safety Signals
The first step in determining whether a product caused a particular adverse event is acquiring complete data from spontaneous adverse event reports, commonly referred to as “case reports.” These reports must be complete and accurate to facilitate a meaningful evaluation of the relationship between the product and adverse events. To help ensure the quality and usefulness of the reports, FDA encourages sponsors to use trained healthcare practitioners to query reporters of adverse events.

According to FDA, good case reports include the following elements:
• Description of the adverse event or disease experience
• Suspected and concomitant product therapy details, including over-the-counter medications, dietary supplements,
and recently discontinued medications
• Patient characteristics
• Documentation of the diagnosis of the event
• Clinical course of the event and patient outcome (e.g., hospitalization or death)
• Relevant therapeutic measures and laboratory data throughout event
• Information about response to dechallenge and rechallenge

In some cases, adverse events are associated with medication errors. Case reports involving such errors should also include information about the product, the type of error, the work environment, type of personnel involved, and contributing factors.

Investigating Safety Signals

The Initial Investigation

If one or more cases suggest that a safety signal warrants additional investigation, sponsors should respond appropriately. This does not mean that sponsors should immediately deploy all available resources at the first sign of a safety signal. The intensity and method of investigation should be determined by the seriousness of the event reported and by other factors, such as the report’s origin. FDA recommends that sponsors place an emphasis on reviewing serious, unlabeled adverse events, although other events may warrant investigation.

FDA also suggests that sponsors initially evaluate a safety signal generated from post-marketing event reports by reviewing individual cases and then conducting a search for additional cases. A sponsor may find additional reported cases by searching the sponsor’s own databases, FDA’s Adverse Event Reporting System (AERS), or other available databases. After gathering the necessary information and reviewing cases, sponsors should look for features that may suggest a causal relationship between the use of a product and an adverse event. In making a determination as to which cases suggest a causal relationship, FDA recommends that sponsors not routinely exclude confounded cases (i.e., cases with adverse events that have possible etiologies other than the product at issue). Confounded cases are common among patients, especially those with complicated medical conditions.

Methods of Investigation

There are a variety of methods for investigating safety signals. One method recommended by FDA is the case review approach. For this approach, FDA recommends that sponsors assemble a case series and summarize descriptive clinical information to characterize the potential risk and, if possible, to identify risk factors. A case series generally includes an analysis of several factors, such as clinical and laboratory manifestations and course of the event, demographic information, duration of exposure, and other information that may be useful in assessing risk and evaluating causality.

Sponsors may also use statistical or mathematical tools, or so-called data-mining, to obtain additional information about the existence of an excess of adverse events reported for a particular product. Because FDA recognizes that statistical information does not provide conclusive answers about whether a product caused an adverse event, data mining techniques are not required. Nonetheless, statistics may provide some insight into patterns of adverse events reported for a given product relative to other products in the same class or to all other products.

Safety signals may also be evaluated through carefully designed non-randomized observational studies of the product’s use in the “real world.” The Guidance focuses on three-types of non-randomized studies: (1) pharmacoepidemiologic studies, (2) registries, and (3) surveys.

Pharmacoepidemiologic Studies

Pharmacoepidemiologic studies come in many forms. They may be cohort studies, case-control, case-crossover, or others. Unlike a case series, these studies employ strict protocol, utilize control groups, and test pre-specified hypotheses. Pharmacoepidemiologic studies may allow a sponsor to estimate the relative risk of an outcome associated with a product. A protocol for pharmacoepidemiologic studies usually consists of clearly specified objectives, a critical review of literature, and a detailed description of the research methods used.

Because pharmacoepidemiologic studies are observational in nature, FDA recognizes that they may be subject to confounding and bias, which make results of these studies more difficult to interpret than other types of studies. Thus, investigators should seek to minimize bias and account for possible confounding. One way to account for confounding is to conduct more than one study in more than one environment. It may also be helpful to use different designs. If these steps are taken, consistent results may be evidence that the observed results are accurate. Sponsors are encouraged to communicate with FDA when pharmacoepidemiologic studies are being developed.

Registries

The term “registry,” as used in the Guidance, means:

...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., 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.
Registries allow sponsors to evaluate safety signals identified from spontaneous case reports, literature reports, or other sources. They also facilitate the evaluation of factors that affect the risk of adverse outcomes, such as dose, timing of exposure, or patient characteristics. Whenever possible, FDA recommends that sponsors use a control or comparison group (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). Establishing a registry may not be appropriate in all circumstances. To determine whether to establish a registry, FDA recommends that sponsors consider the types of additional risk information desired, the attainability of that information through other methods, as well as the feasibility of establishing a registry. Like pharmacoepidemiologic studies, registries should use written, well-developed protocol.

Surveys
Surveys obtained from patients or healthcare providers may be useful in gathering information about a number of things, including safety signals and patient or provider knowledge about labeled adverse events. Like pharmacoepidemiologic studies and registries, surveys should be developed using written protocol. Protocol for surveys should provide 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. Sponsors are encouraged to discuss their survey development plans with FDA.

What should you do with all the information?
If, after conducting an investigation, a sponsor determines that a safety signal may represent a safety risk, FDA recommends that the sponsor submit a synthesis of all available safety information and analyses performed to FDA. The submission should include, among other things, 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. Also, if appropriate, the submission should propose steps to further investigate the signal through additional studies and propose risk minimization actions. Once the information is submitted, FDA will make its own assessment of the potential safety risk posed by the safety signal in question.

In cases where unusual safety risks become evident, a pharmacovigilance plan may be appropriate. A “pharmacovigilance plan” is a plan developed by a sponsor that is focused on detecting new safety risks and/or evaluating already identified safety risks. Such a plan goes beyond routine compliance and is designed to enhance and expedite a sponsor’s acquisition of safety information.

Do you need a Pharmacovigilance Plan?
As previously noted, in most cases, routine compliance with FDCA requirements and FDA regulations is sufficient to assess and minimize safety risks. In cases where unusual safety risks become evident, however, a pharmacovigilance plan may be appropriate. A “pharmacovigilance plan” is a plan developed by a sponsor that is focused on detecting new safety risks and/or evaluating already identified safety risks. Such a plan goes beyond routine compliance and is designed to enhance and expedite a sponsor’s acquisition of safety information. Before developing a pharmacovigilance plan, a sponsor should consider several factors, including:

- The likelihood an adverse event represents a potential safety risk
- The frequency with which the event occurs
- The severity of the event
- The nature of the population(s) at risk
- The range of patients for which the product is indicated
- The method by which the product is dispensed

FDA believes that pharmacovigilance plans may be appropriate where an analysis of these factors reveals the existence of serious safety risks or that at-risk populations have not been adequately studied. Sponsors may discuss their safety concerns about a particular product with FDA and may also seek guidance from FDA regarding whether a pharmacovigilance plan is appropriate.

Conclusion
Good pharmacovigilance practices and pharmacoepidemiologic assessment are essential elements of any risk management plan. Following FDA’s recommendations will help sponsors obtain complete and accurate information about safety signals, determine whether signals are indicative of safety risks, and then take steps to minimize risk. Because it is impossible to identify all safety concerns during clinical trials, it is critical that sponsors use postmarketing safety data collection and risk assessment techniques to evaluate and characterize a product’s risk and make informed decisions to minimize such risk.

2. Id.
5. Guidance, at 15.
8. Id.

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