What Is a Safety Signal?

There is variation in the use of the term "signal" in pharmacovigilance. One commonly cited definition is from the Council for International Organizations of Medical Sciences (CIOMS), which defines a safety signal as "information that arises from one or multiple sources (including observations or experiments), which suggests a new, potentially causal association, or a new aspect of a known association between an intervention [e.g., administration of a medicine]and an event or set of related events, either adverse or beneficial, that is judged to be of sufficient likelihood to justify verificatory action." An example of a "new aspect of a known association" would be refinement of an existing safety signal by identifying subgroups of individuals who may be at greater risk (see sidebar). Usually more than a single report is required to generate a safety signal, depending on the seriousness of the event and the quality of the information.

Various factors about an adverse event are considered to determine the existence or strength of a safety signal. These include the frequency, nature/type, time to onset and duration, and presence of documented high-quality rechallenge/dechallenge information of the adverse event. Detecting, or generating, safety signals is generally carried out by pharmaceutical companies, regulatory agencies (such as the FDA), or other government agencies such as the World Health Organization (WHO).

> **Example of New Information on an Already Identified Safety Signal**
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> 1. An oncology drug is associated with a characteristic form of cardiomyopathy (a weakening of the heart muscle sometimes seen with certain types of chemotherapy).
>   - > This was initially identified on the basis of a small number of spontaneous reports.
> 2. Ongoing surveillance is initiated to gather more information about the association.
> 3. The new/additional information obtained through surveillance suggests that the risk for this adverse effect may be especially high in:
>   - > Pediatric patients.
>   - > Patients previously treated with radiation to the chest region.
>   - > Patients receiving a cumulative dose above a certain threshold.

Identifying safety signals: spontaneous reports

Data contained in spontaneous adverse event reports are collected from patients, health care providers, lawyers, health authorities, the medical literature, and other sources. This information is entered by pharmaceutical companies into their safety databases so that first, serious events meeting certain reporting criteria can be reported to regulators in an expedited manner, and, second, the cumulative adverse event data can be analyzed for potential safety signals. Where a spontaneously reported serious adverse event meets expedited reporting criteria, it must be reported to regulatory agencies within the required expedited timeframe.

In addition to reports forwarded by pharmaceutical companies, the FDA also receives reports via its MedWatch system from health care professionals and consumers. The agency forwards these to the manufacturer of the medicine.

What Is a **Safety Signal?** (cont'd)

All spontaneous reports received by the FDA are entered into the Adverse Event Reporting System (AERS), a database designed to support the FDA's post-approval safety surveillance program. AERS contains data for all approved medicines and therapeutic biologic products,* with a goal of providing a vehicle for signal detection by the agency.

The post-approval spontaneous safety reporting systems maintained by pharmaceutical companies and regulatory agencies contain substantially larger volumes of data than pre-approval databases, which are mainly based on clinical study data. Although useful, spontaneous reports have some limitations, which make interpretation of the data difficult.

One consideration is how to interpret the numbers when generating safety signals. Spontaneous report system data do not inherently include true "denominators," a word used to describe the entire population of patients who have taken a drug. For example, if 20 individual safety reports (ISRs) report a specific adverse event when taking drug A, does this represent 20 out of 250 comparable patients using the drug in the real world, or 20 out of 10,000? And if 80 ISRs of that same adverse event are reported for drug B (again, without knowing the relevant denominator for both drugs), how does this compare to drug A?

Another factor is the phenomenon of "masking." The ability to detect a statistically distinctive reporting association depends on the number of ISRs specific to that association relative to the overall reporting of the drug (across all events) and the event (across all drugs). Drug interactions or rare patient characteristics, however, typically show up in relatively small numbers of ISRs. In such instances, one bad medicine can make others look good (when this may not be the case), and a signal's disproportionate effect (even if it is true) will not show up when the numbers are too small to demonstrate significant differences.

Identifying safety signals: other sources

In addition to spontaneous reports, clinical study data, both pre- and post-approval, play a key role in understanding a medicine's benefit-risk profile. Pharmaceutical companies also use this information to detect signals of potential adverse medicine effects. These signals are then evaluated through a careful review of the cases and a search for additional cases, as well as through epidemiology studies, discussed in a separate briefing document in this series ("How Is Epidemiology Used in Risk Management Planning and Safety Assessment?"), available in the Medicine Safety Timeline section and Resource Library at *www.pfizer.com/medicinesafety*. Regulatory agencies and academic researchers may also use databases of clinical study results as a source for identifying safety signals—for example, ClinicalTrials.gov in the U.S. Other useful sources of information include the many databases and registries that are maintained by health agencies worldwide—for example, the WHO Collaborating Center for International Drug Monitoring database in Uppsala, Sweden, the General Practice Research Database in the United Kingdom and health insurance databases in the U.S.

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*<u>http://www.fda.gov/cder/aers/default.htm</u>

Data mining

In addition to the traditional hands-on review of spontaneous cases and other safety information by trained medical personnel, "data mining" may also be carried out. This is the process of applying sophisticated statistical algorithms to large safety databases to determine whether certain adverse events (AEs) are being reported for a medicine with a greater frequency than expected (i.e., a signal of disproportionate reporting, or SDR), based on a statistical model. For example, a score can be generated for a particular AE-medicine combination (e.g., frequency of bleeding disorder with Drug X) and compared with the score for all medicines in the database (i.e., frequency of bleeding disorder across all medicines). When the AE-Drug X score is greater than the AE-all medicine score, a safety signal may have been detected, depending on the clinical context, since such a number in a biological vacuum does not necessarily constitute a signal of suspected causality. Other available tools (varying in degrees of development) include regression analysis, clustering, link analysis, deviation detection, disproportionality measures, and neural networks. These quantitative methodologies go beyond basic signal detection to assess patterns, time trends, and events associated with more complex phenomena such as drug-drug interactions, which may be more difficult to link by manual review.

It is crucial to remember that the mathematical procedures underlying contemporary data mining cannot fully correct or neutralize the limitations of spontaneous reporting system data. An SDR provides a suggestion of increased spontaneous reporting based on a model. Although such models may be useful, it is of course impossible to know with certainty how many reports of a given drug-event combination are expected. While data mining of spontaneous reporting system data can provide indicators of increased reporting, it cannot provide information on the cause of increased reporting, which in addition to (or instead of) causality, may reflect any one or more of numerous reporting artifacts, confounding factors, and/or the play of chance.

Ultimately, no matter how sophisticated the statistical and quantitative tools that are available, qualitative medical review and assessment are necessary to guide the quantitative analysis and evaluation. In other words, clinical context and medical review are required to determine whether a potential adverse event signal that has been identified merits focused analysis. For example, data mining might correspond to:

- Reporting of the treatment indication as an adverse event, or
- A safety issue that is already known and has been fully investigated.

In these instances, further evaluation would not generally be needed.

Investigating safety signals

Potential signals identified through qualitative and/or quantitative methods can be evaluated using more reliable data sources such as observational/pharmacoepidemiologic studies, additional randomized clinical studies, or mechanistic studies.

Safety signals that warrant further investigation include, but are not limited to:

- New adverse events, not currently documented in the product label, especially if serious and in rare untreated populations.
- An apparent increase in the severity of an adverse event that is already included in the product label.
- Occurrence of serious adverse events known to be extremely rare in the general population.
- Previously unrecognized interactions with other medicines, dietary supplements, foods, or medical devices.
- Identification of a previously unrecognized at-risk population, such as populations with specific genetic or racial predisposition or coexisting medical conditions.
- Confusion about a product's name, labeling, packaging, or use.
- Concerns arising from the way a product is used (e.g., adverse events seen at doses higher than normally prescribed, or in populations not recommended, in the label).
- Concerns arising from a failure to achieve a risk management goal.