FAERS Deconstructed: Requirements, Opportunities, and Limitations of the FDA's Public Adverse Event Reports

Not all possible side-effects of a pharmaceutical drug or medical device can be anticipated based merely on preapproval studies. Safety concerns often don't appear until after the treatment or device has been approved and entered the market. Post-marketing surveillance (the monitoring of drugs and devices after they reach the market), or PMS for short, has been pivotal in identifying these safety issues, and regulatory agencies like the FDA have recognised the need for an improved monitoring system that not only eases adverse event reporting but also improves data access and increases transparency.

The FDA Office of Surveillance and Epidemiology (OSE) within the Center for Drug Evaluation and Research (CDER), for example, oversees a system of PMS programmes to identify adverse events that did not occur during the drug approval process. While not all parts of this surveillance system are new, navigating the surveillance landscape and its different components can pose some challenges.

This article looks at the regulatory requirements for adverse event reporting, how reports are collected and analysed by the FDA, the elements of an informative case report, and – importantly – the various limitations to the FDA's Adverse Event Reporting System (FAERS) that need to be taken into account when accessing safety data through the FDA's publically available database.

Regulatory Requirements

The FDA relies heavily (albeit not exclusively) on spontaneous adverse event reporting; in other words, adverse events that are reported to the FDA either directly via the consumer and healthcare professional (HCP) ("Direct Reports") or indirectly via the sponsor who receives reports from HCPs and consumers. For example, for any drug or device on the market, sponsors must submit both 15-Day Alert Reports and Periodic Adverse Experience Reports, according to the Code of Federal Regulations 21 CFR 314.80:

- 15-day Alert Reports, which are categorised as "Expedited Reports", have to be submitted within 15 days of each adverse event that is both serious and unexpected. (Serious events are those that result in death, life-threatening experiences, hospitalisation, disability, birth defects, and other outcomes that require medical intervention.) The sponsor is then required to follow up with an investigation and submit a "follow-up report" no later than 15 days after the initial report.
- All other events that are not both serious and unexpected (serious and expected, non-serious and unexpected, non-serious and expected) have to be reported at quarterly intervals during the first three years and then annually in the form of Periodic Adverse Experience Reports (categorised as "Non-Expedited Reports").
- While Periodic Reports only include domestic events, 15-day Alert Reports have to include adverse events that occur both in the US and abroad.

In addition to adverse event reports, the FDA also expects drug manufacturers to "submit either error and accident reports or drug quality reports when deviation[s] from current good manufacturing practice regulations occur."

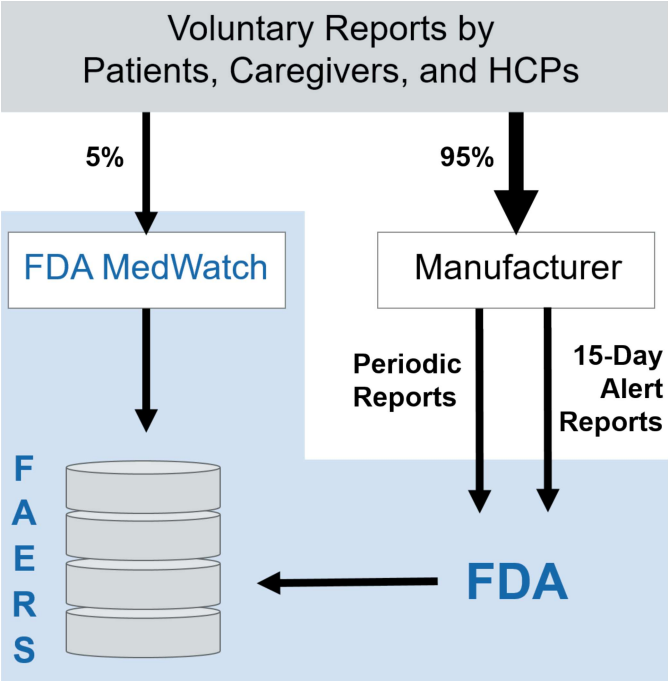

Figure 1. 95% of Adverse Event Reports reach the FDA via the manufacturer, while the remaining 5% enter the system directly via FDA MedWatch.

Tracking Adverse Events

Keeping track of the various spontaneous event reports is the FDA's Adverse Event Report System (FAERS), which supports the agency's post-marketing safety surveillance programme for all approved drug and therapeutic biologic products. Dating back to 1969, this fully digital, automated database contains nearly 16 million reports on human drugs and therapeutic biologics, 1.81 million of which were filed in 2017 alone. Roughly 95% of these reports reach the FDA via the manufacturer, while the remaining 5% enter the system directly via FDA MedWatch, a programme that allows healthcare professionals (physicians and pharmacists) and the public to voluntarily report serious issues with medical products.

A Dashboard for All

Earlier this year, the FDA launched the FAERS Public Dashboard, a highly interactive online tool that expands FAERS data access to the general public in a user-friendly manner, offering, among other things, more options for efficiently filtering and organising data on adverse events within a chosen timeframe. For example, the dashboard allows users to display reports by a wide range of criteria for all reports submitted since 1969, including report type, reporter, reporter region, and report seriousness. Users can also search for certain products or reactions. Quarterly updates to the dashboard ensure that users can view information that is no more than three months old; however, users should be aware

that more recently submitted information won't be visible until the next update.

Review and Analysis: Generating Safety Signals

Clinical reviewers in the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) regularly evaluate FAERS reports as well as other safety data resources to monitor the safety of drugs and biologics after they entered the market. The Division of Pharmacovigilance – one of the divisions of the FDA OSE – has nine teams of safety evaluators, who evaluate the safety of drugs and therapeutic biologic products, as well as medical officers, who provide clinical expertise across therapeutic areas. Using FAERS data, these teams identify safety concerns and – after further evaluation using additional data available in, e.g., the Sentinel System – may recommend regulatory actions to protect public health.

For the analysis of safety reports, reviewers use specific data mining methods and analysis tools. Certain statistical tools, for example, will generate so-called "safety signals" based on the submitted reports, helping reviewers identify potential causal relationships between products and adverse events, new at-risk populations, interactions, and unlabelled events, as well as increased occurrence or severity of a labelled event. These data then provide the basis for further studies on the part of the FDA, which typically involve literature reviews, consultation with other clinical experts, and mining health claims data contained within the Sentinel System, as well as other large healthcare databases. Depending on the findings, the FDA may then take important regulatory steps to ensure the safety and health of the public, such as updating the product's labelling information, restricting the use of the drug, communicating new safety information to the public, or, in some cases, removing a product from the market.

What Should An Informative Case Report Contain?

Case reports are required to include information about the patient, medical product, adverse event, and reporter. The most informative case reports describe these four required elements in more detail, elaborating, among other things, on different patient characteristics (age, sex, medical and family history, comorbidities, and other risk factors); type, duration, and dosage of the drug as well as of any other medications used; the diagnosis; and the clinical course and outcome of the adverse event. Reports should also include laboratory results and describe therapeutic measures taken during the adverse event. Another important element is a description of any positive or negative dechallenge (symptoms disappearing after drug withdrawal) and rechallenge (symptoms re-appearing after drug re-administration).

Handling FAERS Data with Care

Once on the market, there is a continuous need for understanding the benefit-risk profile of an approved drug. In the real world, the drug is being used by a patient population that, typically, is much different and significantly more heterogeneous than the population studied under the strict criteria of clinical study protocols. In addition, real-world patients may suffer from other serious medical conditions, and they may take the medical product for chronic rather than short-term uses that far exceed the duration of clinical trials.

Post-marketing monitoring, on the other hand, can complete the picture of how a drug affects real-world patients under various conditions. Surveillance systems like FAERS can not only reveal rare adverse events but also adverse events in high-risk groups and after long-term use as well as drug-drug or drug-food

interactions. Another strength of FAERS is that reports can be submitted for both old and new drugs, and regardless of whether causality is certain.

Limitations

Although FAERS is a treasure trove of information that emerges from realistic healthcare settings, there are also important limitations to the voluntarily submitted data in these reports that could lead some to draw false conclusions. First and foremost, the FDA emphasises that the presence of a report does not imply causation (in other words, it is not proof of the drug causing the adverse event), and that the data by themselves are not an indicator of the safety profile of the drug or biologic. What's more, with an open-for-all, voluntary system of data submission, there are a number of data quality issues that should be considered when consulting FAERS data, including the potential for duplicate, incomplete, or inaccurate reports, unverified data, reporting biases, and underreporting for some drugs versus others. FAERS reports also cannot be used to estimate the prevalence of a side-effect, because there is no information on how many patients took the drug. Instead, the FDA uses dispense information from other sources to appropriately estimate incidence rates.

It's also important to consider the various factors that can affect reporting. Media attention, class action lawsuits, and the type of adverse event can significantly impact the nature and number of submitted reports. Other factors include how long the product has been on the market, whether it's a prescription or over-the-counter drug, and how the manufacturer conducts surveillance of its products.

While a FAERS report is not evidence for cause and effect, it's certainly an important source of new findings that may provide a "signal" that should be looked at more closely to ensure the safety and health of the public. Indeed, a large part of the new safety findings that the FDA announces and the regulatory actions it takes are based on safety signals generated from FAERS.

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