

Drug and Biologics Safety Surveillance Best Practice Statement
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
US Food and Drug Administration

The 21st Century Cures Act (the “Cures Act”), enacted on December 13, 2016, has the goal of advancing medical product innovation as well as ensuring patient access to safe and effective treatments as soon as possible. One of the provisions of the Cures Act includes a revision to a previous statutory requirement that generally required FDA to undertake routine safety analyses of drugs 18 months following approval or after 10,000 individuals have used the drug, whichever occurs later. See section 505(r)(2)(D) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) before and after it was amended by the Cures Act. These assessments were largely redundant to our current surveillance practices at the Food and Drug Administration (FDA), were not an efficient use of FDA resources, and did not provide sufficient flexibility to take a risk-based approach based on various factors, including the characteristics of products or their projected use. For example, many drugs and biological products for rare diseases never met the 10,000-individual use threshold triggering these analyses. The Cures Act replaced the previous 18-month/10,000 patient analysis with a new requirement that FDA make publicly available on the internet its best practices for drug safety surveillance activities for drugs approved under section 505 of the FD&C Act or licensed as biological products under section 351 of the Public Health Service Act.

This document sets forth risk-based principles by which FDA conducts ongoing drug and biological product safety surveillance. As such, and consistent with the Cures Act, FDA will follow these principles in lieu of performing or posting the previously required safety analyses at 18 months or after 10,000 patients have used the drug. A more detailed best practice of drug and biological product safety surveillance document describing this process is under development and will be made available for public comment.

FDA is responsible for protecting the public health, which includes assuring the safety of drugs and biological products. One of the ways this mission is accomplished is by the prompt detection and assessment of safety concerns associated with drugs and biological products following FDA approval. FDA uses multiple sources of information to detect and assess potential new postmarket safety issues, including:

- Spontaneous adverse event and medication error reports submitted by patients, family members, healthcare providers, and manufacturers
- Clinical trials and epidemiological studies conducted following approval (commonly referred to as “postmarketing studies”)
- Descriptions or studies of safety issues in the peer-reviewed medical literature
- Periodic Safety Reports that manufacturers are required to submit to FDA
- Information from other national regulatory authorities

- Drug and biological product utilization information

Each of these sources of information has specific strengths and limitations. For instance, clinical trials are able to provide highly detailed information about enrolled patients, but may not be able to detect rare safety problems due to the practical limitations on trial size. Spontaneous adverse event reporting systems, such as the FDA Adverse Event Reporting System (FAERS) and Vaccine Adverse Event Reporting System (VAERS), can detect rare problems, but reports may be missing important information. Additionally, the frequency of reports to spontaneous adverse event reporting systems is not a reliable indicator of the frequency of an event due to uncertain exposure estimates, under-reporting as well as stimulated reporting, such as when there is extensive media coverage for a safety issue. Observational studies can help to provide insight into the safety of a product during actual, real-world use by providers and patients, but can be difficult to interpret due to potential biases and confounding factors. FDA monitors and assesses available safety data from all sources of information to detect changes in the known safety profile and to identify new safety issues.

The frequency and type of systematic monitoring and assessment for drug and biological products are determined by the product characteristics and intended population. This is influenced by factors such as:

- Duration of time that the product has been on the market. For instance, products on the market for longer periods of time generally are less likely to have new safety findings.
- Complexity of the product's manufacturing process and the product's composition.
- Whether the dose of the product needed to produce its intended beneficial effect is close to a dose that can cause safety issues.
- Use in special populations (e.g., during pregnancy, in children, or in elderly patients).
- Products with novel mechanisms of action for which safety issues are less predictable.
- Accelerated approvals where there may be less information about the occurrence of rare or delayed adverse events.

Factors that may signal the need for enhanced safety monitoring and assessments may include:

- Reports involving death or other types of serious or unexpected safety issues that may impact the public health
- Safety issues that historically are known to be likely related to a product, such as hypersensitivity reactions including anaphylaxis
- Important potential risks of the product recognized at the time of or after approval
- Safety issues that are biologically plausible based on a product's known pharmacological action

Additional safety assessment measures may include the initiation of postmarketing safety studies conducted by FDA and/or the product manufacturer. Safety studies can include studies using healthcare data such as the Sentinel System, patient registries, clinical trials, or other appropriate data sources.

With these best practice safety surveillance principles, FDA continues its commitment to rigorous, risk-based postmarketing safety surveillance of all drugs and biological products, and to the protection of public health.