Best Practices in Drug and Biological Product Postmarket Safety Surveillance for FDA Staff

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1. Executive Summary

This document,[1] *Best Practices in Drug and Biological Product Postmarket Safety Surveillance for FDA Staff*, sets forth risk-based principles by which the Food and Drug Administration (FDA or Agency) conducts ongoing postmarketing safety surveillance for human drug and biological products (biologics). The main topics this document addresses include:

- A multidisciplinary, life-cycle approach to the management of drug and biologic safety.
- General considerations that inform the frequency and extent of systematic drug and biologic safety monitoring (section 4).
- Additional considerations based on specific product types and patient populations (section 5).
- Safety signal identification based on screening and data mining of the adverse event (AE) reporting system and other data sources, including general practices for the frequency and extent of screening these data sources, as well as prioritizing identified signals (section 6).
- A multidisciplinary, comprehensive evaluation of the identified safety signal that integrates the cumulative data gathered from all available sources (section 7).
- An assessment of the causal association between the identified AE and the product (section 8).
- An overview of regulatory and other actions that can be taken in response to identified safety signals (section 9).

2. Introduction

2.1. Regulatory History

Title IX, section 915 of The Food and Drug Administration Amendments Act (FDAAA) of 2007 added a new section 505(r) to the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355(r)),[2] requiring FDA to prepare—

> . . . by 18 months after approval of a drug or after use of the drug by 10,000 individuals, whichever is later, a summary analysis of the adverse drug reaction reports received for the drug, including identification of any new risks not previously identified, potential new risks, or known risks reported in unusual number.[3]

FDAAA also added a new subsection (k)(5) to section 505, which required FDA to—

> conduct regular, bi-weekly screening of the Adverse Event Reporting System database and post a quarterly report on the Adverse Event Reporting System Web site of any new safety information or potential signal of a serious risk identified by Adverse Event Reporting System within the last quarter.[4]

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[1] This document was prepared by the Office of Surveillance and Epidemiology, in collaboration with other offices in the Center for Drug Evaluation and Research and with the Center for Biologics Evaluation and Research, at the Food and Drug Administration.

[2] http://www.gpo.gov/fdsys/pkg/USCODE-2010-title21/html/USCODE-2010-title21-chap9-subchapV-partA-sec355.htm.

[3] Ibid.

[4] Ibid.

The 21st Century Cures Act[5] (Cures Act) was enacted on December 13, 2016, and has the goal of advancing medical product innovation, as well as ensuring patient access to safe and effective treatments as soon as possible. Section 3075 of the Cures Act amended section 505(r)(2)(D) of the FD&C Act to eliminate the requirement for summary analyses for drugs as required by FDAAA. In place of the summary analyses, section 3075 amended section 505(r)(2)(D) of the FD&C Act to include the requirement that FDA make publicly available on its internet website ". . . best practices for drug safety surveillance activities for drugs approved under this section or section 351 of the Public Health Service Act."

Section 3075 of the Cures Act also amended section 505(k)(5) of the FD&C Act to strike "bi-weekly screening," as required by FDAAA, and insert "screenings"; it also added the requirement that FDA make publicly available on its internet website the following:

> (i) guidelines, developed with input from experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, that detail best practices for drug safety surveillance using the Adverse Event Reporting System; and
>
> (ii) criteria for public posting of adverse event signals.

2.2. Scope and Goals of This Document

As its primary focus, this document sets forth risk-based principles by which FDA conducts ongoing postmarketing safety surveillance for drug and biological products to address the Cures Act requirements to develop and make publicly available best practices and guidelines related to drug safety surveillance. Although section 3075 of the Cures Act only references drugs approved under section 505 of the FD&C Act or section 351 of the Public Health Service Act (PHS Act), this document additionally discusses other products, including over-the-counter (OTC) monograph, compounded, and homeopathic products.[6] It also includes a high-level overview of other data sources, tools, and methods, as well as drug safety surveillance activities that extend beyond use of the Adverse Event Reporting System (and its successors). These additional topics are included to provide context and a general overview of FDA's safety surveillance process.

The drug safety surveillance principles and best practices detailed in this document build upon lessons learned in preparing and publicly posting the summary analyses of adverse drug reaction reports previously required under section 505(r) of the FD&C Act. FDA conducted a study to assess the impact of these summary analyses on regulatory actions.[7] In interpreting the study findings, FDA determined these summary analyses were largely redundant to the surveillance practices in place at the time FDAAA

[5] https://www.congress.gov/114/bills/hr34/BILLS-114hr34enr.pdf.

[6] Biological products discussed in this document are limited to those with approved BLAs for which manufacturers are required to submit adverse experience reports under 21 CFR 600.80. Pharmacovigilance considerations for other biological products (e.g., whole blood and blood components, which are exempt from 21 CFR 600.80) are not discussed in this document.

[7] Sekine S, Pinnow EE, Wu E, et al. Assessment of the impact of scheduled postmarketing safety summary analyses on regulatory actions. *Clin Pharmacol Ther*. 2016;100(1):102-108.

took effect and were not an efficient use of FDA resources. Furthermore, many drugs and biological products for rare diseases never met the 10,000-individual use threshold.

2.3. Related Documents

The Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) maintain procedural documentation for various internal practices for evaluation of drugs (i.e., CDER's Manual of Policies and Procedures[8] (MAPP), CDER's Standard Operating Procedures,[9] and CBER's Standard Operating Procedures and Policies[10] (SOPPs)). FDA also issues many guidance documents to industry, all of which are posted on the FDA website; FDA maintains a web page of those that relate specifically to drugs.[11]

FDA is also developing internal, supporting technical documents to guide the implementation of the principles articulated in this best practice document.

2.4. Terms Referenced Throughout Document

An *adverse drug experience* is any *adverse event* (AE) associated with the use of a drug in humans, whether or not considered drug related, and includes the following: an AE occurring in the course of the use of a drug product in professional practice; an AE occurring from drug overdose whether accidental or intentional; an AE occurring from drug abuse; an AE occurring from drug withdrawal; and any failure of expected pharmacological action.

FDA also monitors AE reports to detect cases of medication errors. The strategies for AE surveillance are generally the same for medication error pharmacovigilance, with some exceptions noted as applicable in this document. Excluding these exceptions, all references to *adverse event* include *medication error*.

The term *AE of interest* is used to describe an AE that reviewers would closely monitor during surveillance based upon biological plausibility or known class effect, as well as signals identified from any source that upon evaluation warrant close monitoring.

FDA uses the term *signal* to mean information that arises from one or multiple sources (including observations and experiments), that suggests a new potentially causal association, or a new aspect of a known association, between an intervention and an event or set of related events, either adverse or beneficial, that is judged to be of sufficient likelihood to justify further action to verify.[12] Because this

[8] A listing of CDER MAPPs is available at https://www.fda.gov/about-fda/center-drug-evaluation-and-research/cder-manual-policies-procedures-mapp.
[9] MAPP 4001.1, describing the policy for developing, issuing, and maintaining SOPs for CDER is available at https://www.fda.gov/media/90280/download.
[10] A listing of CBER SOPPs is available at http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/ProceduresSOPPs/default.htm.
[11] https://www.fda.gov/drugs/guidance-compliance-regulatory-information/guidances-drugs.
[12] The guidance for industry *E2C(R2) Periodic Benefit-Risk Evaluation Report (PBRER)* is available at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

document focuses on safety surveillance, the term *signal* is used herein to describe adverse (and not beneficial) events.

Acronyms used in this document are defined at first use and are listed in section 11.

3. FDA's Adverse Event Reporting Systems

FDA's adverse event reporting systems are designed to support postmarketing safety surveillance programs for drug and biological products.

The FDA Adverse Event Reporting System[13] (FAERS) is a database that contains individual case safety reports (ICSRs) of AEs. ICSRs in the FAERS database provide critical information to FDA during ongoing product safety surveillance in the postmarketing period.

The Vaccine Adverse Event Reporting System[14] (VAERS) is an analogous database that underpins the national program jointly managed by the U.S. Centers for Disease Control and Prevention (CDC) and FDA to monitor the safety of vaccines licensed in the United States. VAERS accepts and CDC and FDA analyze information from reported AEs that occur after vaccination. The National Childhood Vaccine Injury Act (NCVIA) (42 U.S.C. 300aa-25) mandates that health care providers and vaccine manufacturers report certain specified vaccine events, as well as any event that is listed in the manufacturer's package insert as a contraindication to the vaccine.[15,16]

FDA receives ICSRs from two main sources: the regulated industry and the public. ICSRs from industry are sent to FDA on a mandatory basis by applicants, licensed manufacturers, packers, distributors, and responsible persons[17] subject to FDA's requirements for postmarketing safety reporting.[18,19] Members of the general public, including health care providers, patients, consumers, and family members, have two avenues to voluntarily report an AE—they may report it to the applicant or they may report directly to

[13] More information about FAERS is available at https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm.
[14] More information about VAERS is available at https://vaers.hhs.gov/index.
[15] Although most AE reporting is voluntary for health care providers, health care providers are required to report some AEs for vaccines. Vaccine Safety Questions and Answers are available at https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/vaccine-safety-questions-and-answers.
[16] The VAERS Reportable Events Table lists the events that are reportable by law under NCVIA and is available at https://vaers.hhs.gov/docs/VAERS_Table_of_Reportable_Events_Following_Vaccination.pdf.
[17] "Responsible persons" is the term used for the manufacturer, packer, or distributor whose name appears on the label of an OTC drug marketed in the United States without an approved application and who has AE reporting responsibilities under section 760 of the FD&C Act.
[18] Reporting regulations for products addressed in this document are found in 21 CFR 310.305 (prescription drugs marketed for human use without an approved application); 21 CFR 314.80 (human drugs with approved NDAs); 21 CFR 314.98 (human drugs with approved ANDAs); 21 CFR 600.80 (human biological products with approved BLAs), and section 760 of the FD&C Act (nonprescription human drug products marketed without an approved application).
[19] For the purposes of this document, applicants, licensed manufacturers, packers, distributors, etc., are hereafter referred to as *applicants* except when referring to unapproved products, in which case *manufacturer* is used.

FDA (or the VAERS program in the case of vaccines). If a member of the public reports an AE to the applicant, then the applicant must report the AE to FDA in accordance with regulatory requirements.

4. Risk-based Approach to Drug Safety Surveillance

Consistent with the mission to protect and advance the public health, FDA monitors the benefit-risk balance of products over their life cycle and takes regulatory action(s) when appropriate. FDA's safety surveillance begins early in the product's life cycle as part of the review process that may lead up to FDA approval. Once a marketing application for a product is filed, a multidisciplinary team is formed to evaluate the application, including considering appropriate measures to continue to assess the safety of the product if and when it gains FDA approval. Members of the multidisciplinary team have expertise in medicine, pharmacology, epidemiology, safety surveillance, medication error prevention, risk management, product quality, and statistical analysis.

It is not possible to identify all risks of a product during the clinical trials conducted as part of that product's development. Once a product is approved and marketed, new information about the safety of the product may be learned. For example, after approval and marketing, many more patients will be exposed to the product, including more patients with comorbid conditions and on concomitant medical products, providing more information. Together, the FDA multidisciplinary team determines the postmarketing surveillance strategy and activities on a product-specific basis using a risk-based approach. The team also provides expert input to identify what additional activities, if any, an applicant must perform in the postmarketing period.

Once FDA approves a product, a risk-based postmarketing safety surveillance phase begins and continues for the life of the product. The principles of risk-based safety surveillance include considerations of the product's characteristics and use in a manner that informs the frequency and extent of systematic monitoring. Products that generally are subject to more extensive monitoring include:

- NDAs that are new molecular entities.
- Original biological license applications (BLAs).
- Biosimilar biological products.
- First in class approvals.
- Newly approved formulation(s).
- Newly approved indication(s).
- Extension into new patient populations.
- Products with complex pharmacokinetic (PK) or pharmacodynamic (PD) characteristics.
- Products with complex compositions or manufacturing processes.

Reviewers also monitor the safety of compounded products, even though they are not subject to FDA premarket review and approval, as well as homeopathic products.

When conducting surveillance, reviewers focus on information that suggests a safety signal or broadly describes safety concerns (i.e., important identified risk(s), important potential risk(s), and important

missing information)[20] for the product under evaluation. Safety information of interest to reviewers during surveillance includes the following:[21]

- Important potential risks of the product recognized at the time of or after approval.
- Apparent increase in the severity or frequency of reporting of a labeled AE.
- Deaths, particularly in populations or in patients using the product for indications for which there would not be the expectation of death.
- AEs for which causal attribution to the product is biologically plausible, based on the product's known pharmacological action.
- Reports of unlabeled, serious AEs.[22]
- Serious AEs thought to be rare in the general population and associated with a high product-attributable risk.
- Interactions among different products (e.g., drug-drug, drug-device, drug-food, or drug-dietary supplement).
- Reports of reduced effectiveness or efficacy.
- Medication errors[23] resulting from confusion about a product's name, labeling, packaging, or use.
- Off-label use, misuse, abuse, and other intentional uses of a product in a manner that is inconsistent with the FDA-approved labeling.
- AEs reported or observed in a specific patient population.
- AEs for which a Risk Evaluation and Mitigation Strategy (REMS) is intended to mitigate the risk.

5. Special Topics in Drug and Biological Product Safety Surveillance

5.1. Biological Products

Biological products (also called "biologics") include products that are isolated from a variety of natural sources including humans, animals, and microorganisms. Examples of biologics include vaccines, gene therapies, allergenic extracts, cellular therapies, and blood-derived and recombinant therapeutic biologics, such as monoclonal antibodies, immune globulins, clotting factors, and enzyme replacement proteins. Biologics that are demonstrated to be biosimilar to or interchangeable with FDA-approved biologics are discussed in subsection 5.1.1, below.

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[20] The ICH E2E Guidance describes a method for summarizing important risks and is available at https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073107.pdf.

[21] For additional information, see the guidance for industry *Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment* at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

[22] FDA applies the definition of serious in 21 CFR 314.80(a) and 600.80(a). A serious adverse drug experience results in any of the following five outcomes: death, a life-threatening adverse drug experience, hospitalization (inpatient or prolonged), persistent or significant disability/incapacity, or congenital anomaly/birth defect. Other important medical events may be considered to be serious adverse experiences when they may jeopardize a patient and required intervention to prevent one of the listed outcomes.

[23] Special considerations regarding medication errors are discussed in section 5.8 of this document, including the definition used by FDA.

AE reporting practices and regulations for biological products licensed under section 351 of the Public Health Service Act, including vaccines, are similar to those for drugs approved under section 505 of the FD&C Act, and the pharmacovigilance practices discussed in this document generally apply to biologics as well. However, there are issues specific to biologics that need to be addressed when monitoring postmarketing safety. These issues include immunogenicity, product manufacturing variability, and risk of product contamination with infectious agents.

Immunogenicity as a safety concern in therapeutic biological products

Most biologics elicit immunological responses to some extent following human administration,[24] which may result in specific AEs generally not seen with small molecule drugs. The following immunological issues are specifically monitored during the safety surveillance of biologics:

- Anaphylaxis and other hypersensitivity reactions—allergic reactions can occur with therapeutic biologics, although the frequency may be insufficient to allow detection during premarket development. All routine and aggregate analyses of each product's postmarketing safety evaluation generally include monitoring of AE terms that indicate anaphylaxis or other allergic reactions.
- Immune complex disease—the immunogenicity of a therapeutic biologic may result in large complexes of the therapeutic biologic in combination with antibodies, resulting in what is known as immune complex disease. Such complexes may accumulate in organs, resulting in organ dysfunction.
- Loss of efficacy—therapeutic biologics can stimulate an immune response against the biologic itself through the production of anti-drug antibodies; this immune response can lead to a decrease in effectiveness of the therapy over time.
- Human protein analogs—administration of therapeutic biologics that are similar to human proteins can, in rare cases, lead to breakage in immune tolerance. That is, some patients who receive such products can develop an immune response to the natural human protein, which may result in sustained loss of function of the protein, even after discontinuation of the therapeutic biologic.
- Off-target binding—in addition to the intended site of action, therapeutic biologics may rarely bind to other tissues, which may cause an AE due to stimulation of an inappropriate immune response.

Product manufacturing variability

The structure of biologics is typically larger and more complex than that of other drugs, and the manufacturing process is generally more complex. Additionally, because some source materials are derived from biological materials, there can be naturally occurring variabilities in the characteristics of these materials with each batch of product. While manufacturers control the process to manage the risks and minimize product variability, product quality issues (PQIs) may still occur. Therefore, when lot information is available during postmarketing surveillance, it can be useful in identifying potential manufacturing issues and in analyzing AEs by lot number.

[24] Wadhwa M, Thorpe R. Unwanted immunogenicity: lessons learned and future challenges. *Bioanalysis*. 2010;2(6):1073-1084.

Product contamination

Another complexity of biological products is that manufacturing may include biological systems. In certain cases, there is a potential for source material to be contaminated with infectious agents, and surveillance for infections may be appropriate as part of routine monitoring. Therefore, safety monitoring for these products should routinely include surveillance for infections.

5.1.1. *Biosimilar Products*

The Biologics Price Competition and Innovation Act of 2009 amended the PHS Act and other statutes to create an abbreviated licensure pathway in section 351(k) of the PHS Act for biologics shown to be biosimilar to or interchangeable with an FDA-licensed biological reference product.[25] FDA applies the same surveillance principles for biosimilar products as for NMEs and for originator biological products licensed in a "stand-alone" biologics license application (BLA) under section 351(a) of the PHS Act. On a product-specific basis, reviewers consider the biosimilar product's safety profile, product characteristics, manufacturing process, and licensed conditions of use, as is the case for NMEs and biological products licensed under section 351(a) of the PHS Act.

A newly identified, serious AE may be specific to the particular biosimilar product or it may be associated with the class of biologics that has a common biological target or effect. Therefore, reviewers include a review of data on the reference product as part of the evaluation of the AE to help determine whether the AE is associated with the specific biosimilar product, as opposed to the class of products. Report-level analysis is carried out to identify unusual or unique clinical presentations of labeled AEs. A high index of suspicion is maintained for clinical events reported for the biosimilar product that are not consistent with the safety profile of the reference product. Data mining of FAERS reports for the biosimilar product and the reference product is another approach to identify potential signals and AEs reported disproportionately for the biosimilar product.

AEs pertaining to biosimilar products may be reported to FDA by proprietary name or nonproprietary name. The reporter may inadvertently use the reference product's proprietary name or nonproprietary name to identify the biosimilar product. Reviewers keep these potential reporting limitations in mind to avoid misattributing the reported AE(s). Reviewers are encouraged to review the narrative report, as it may contain more information about the identity of the reported product.

5.2. Generic Drugs

FDA follows a rigorous review process to make sure that, compared to the reference listed drug (i.e., brand name or innovator), a generic drug, with limited permissible exceptions, has the same active ingredient(s), strength, dosage form (e.g., a tablet, capsule, or liquid), route of administration (e.g., oral, topical, or injectable), labeling, and conditions of use.[26] Generic drug surveillance follows a multidisciplinary process built upon continuous collaboration in monitoring and analyzing all available postmarketing AE safety data.

[25] Additional information is available at https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/ucm215089.htm.

[26] 21 CFR 314.92(a)(1).

Although innovator and generic drugs have the same active ingredients, there may be permissible differences in formulations, excipients, release technologies, or device components between innovator and generic drugs that pose unique challenges for pharmacovigilance activities. As such, safety surveillance for generics includes processes for detecting AEs possibly related to excipients and other product quality differences between innovator and generic drugs, as well as other unexpected or rare events that become apparent with increasing exposure to an active ingredient (of innovator and generic products) in a larger and potentially more diverse patient population.

Due to familiarity with drug brand names, when members of the public report an AE associated with use of a generic drug, they often submit a report to FDA that lists the brand-name drug, or they report the event directly to the innovator manufacturer. In addition, when there are multiple generics on the market, the reporter may not know which specific generic drug is involved and thus list the innovator product. Based on the reported information, reviewers may have great difficulty determining whether the drug used was the innovator drug or a generic. These shortcomings in ICSR quality can lead to misattribution of generic-associated AEs to brand-name drugs, which can limit the reviewer's ability to accurately trace the reported AEs to the associated drug.[27]

One concern for all products is therapeutic failure. In addition, reports that a generic product is not therapeutically equivalent to its reference product are of concern for generic drugs. A potential absence of therapeutic equivalence may present as a perceived increase or decrease in the therapeutic effect when a patient is switched from an innovator to a generic drug, or from one generic drug to another. Reviewers screen for persistent or increasing reports that suggest that a single generic product may not be therapeutically equivalent to its reference listed drug, excessive numbers of reports in proportion to the distribution of a particular generic, or evidence that a generic does not have a significant clinical impact, including medication use errors.

Other concerns relate to the complexity of the generic drug or risks associated with differences in the user interface of a generic drug compared to the innovator. Reviewers may focus their surveillance of generic products on solid oral products with modified-release mechanisms, drug-device combination products (e.g., injectables, depot formulations, and transdermal formulations), products with a narrow therapeutic index, and products with active ingredients that have highly correlated PK-PD relationships. Signals that are suggestive of a potential quality issue with a generic product are evaluated in a collaborative process with other FDA offices and in the context of other available data streams including, but not limited to, product distribution data and Field Alert Reports.

Reviewers also evaluate serious AEs from expedited safety reports from bioavailability/bioequivalence studies.[28,29] These important expedited safety reports could reflect a problem with the generic drug formulation, subject inclusion/exclusion criteria, or other aspects of the study design. Reviewers evaluate these initial and follow-up expedited safety reports, request additional information from submitters when

[27] Bohn J, Kortepeter C, Muñoz M, et al. Patterns in spontaneous adverse event reporting among branded and generic antiepileptic drugs. *Clin Pharmacol Ther*. 2015;97:508–517.
[28] 21 CFR 320.31(d)(3).
[29] The guidance for industry and investigators *Safety Reporting Requirements for INDs and BA/BE Studies* is available at https://www.fda.gov/drugs/guidancecomplianceregulatoryinformation/guidances/default.htm.

needed, determine probable study-related risks to subjects, and formulate appropriate recommended actions.

5.3. Over-the-Counter Drugs

In general, OTC drugs are marketed in the United States under either the monograph system, a new drug application (NDA), or an abbreviated new drug application (ANDA). For those OTC drugs marketed under an NDA or ANDA, there is a regulatory requirement for manufacturers to submit AE reports, including periodic safety reports (PSRs)[30] to FDA. PSRs can provide a useful source of information for estimating exposure data for an OTC drug and for identifying trends in AE reporting. Unapproved OTC drugs, including those marketed under the monograph system do not have a corresponding requirement for periodic reporting, although they are subject to certain reporting requirements for serious AEs.

Surveillance of OTC products containing active ingredients that are also included in prescription drug products necessitates the involvement of other offices that have regulatory oversight for these products. Once a safety signal is identified for any OTC product, a multidisciplinary process is followed to consider changes to the OTC product labeling and other regulatory actions as appropriate.

5.4. Orphan Drugs and Drugs for Rare Diseases or Conditions

The Orphan Drug Act provides for granting orphan designation to a drug or biologic that is intended for use in a rare disease or condition, which is defined as a disease or condition that affects fewer than 200,000 people in the United States or that affects more than 200,000 people in the United States, but there is no reasonable expectation to recover the costs of developing and marketing a treatment drug.[31] While approval for all drugs and biologics—for both rare and common conditions—must be based on demonstration of substantial evidence of effectiveness and a favorable benefit risk balance, FDA recognizes that certain aspects of product development that are feasible for common diseases may not be feasible for rare diseases. Many rare disorders are serious conditions with no approved treatments, leaving substantial unmet medical needs for patients.[32] FDA regulations provide flexibility in applying regulatory standards for drug approval because of the many types and intended uses of drugs.[33] This flexibility extends from the early phases of development to the design of adequate and well-controlled clinical studies that are required to demonstrate safety and effectiveness to support marketing approval.

The goal of safety evaluation during drug development is to characterize the drug's safety profile in a reasonable number of patients over a reasonable duration of time, consistent with the intended use of the drug. "Reasonable" in the context of rare diseases requires consideration of feasibility challenges posed by the limited number of patients with the disease. The amount of safety information at the time of

[30] Periodic Safety Reports include periodic adverse drug experience reports (21 CFR 314.80) and periodic adverse experience reports (21 CFR 600.80) and, under an approved waiver, International Council for Harmonisation reporting formats (periodic safety update report and periodic benefit risk evaluation report).
[31] Section 526 of the FD&C Act provides for the designation of drugs for rare diseases or conditions. Available at https://www.gpo.gov/fdsys/pkg/USCODE-2010-title21/html/USCODE-2010-title21-chap9-subchapV-partB-sec360bb.htm.
[32] The draft guidance for industry *Rare Diseases: Common Issues in Drug Development* is available at https://www.fda.gov/drugs/guidancecomplianceregulatoryinformation/guidances/default.htm. When final, this guidance will represent the FDA's current thinking on this topic.
[33] 21 CFR 314.105.

approval may be less for drugs developed for rare diseases when compared to those for common diseases, given the limited study population. The postmarketing period frequently provides additional safety information, as the number of patients exposed slowly increases over time, or through a specific postmarketing requirement or commitment. Once a safety signal is identified, a multidisciplinary process is followed to consider changes to the product labeling and other regulatory actions as appropriate.

5.5. Compounded Drugs

Compounding is generally a practice in which a licensed pharmacist, a licensed physician, or, in the case of an outsourcing facility, a person under the supervision of a licensed pharmacist combines, mixes, or alters ingredients of a drug to create a medication tailored to the needs of an individual patient.[34] Compounded drugs are not approved by FDA.

Under section 503A of the FD&C Act, compounded drugs that meet certain conditions are exempt from FD&C Act sections on premarket approval, current good manufacturing practice (CGMP) requirements, and labeling with adequate directions for use if the drug is compounded for an identified individual patient based on a valid prescription. This practice is sometimes referred to as traditional compounding. State boards of pharmacy have primary responsibility for the day-to-day oversight of State-licensed pharmacies that compound drugs in accordance with the conditions of section 503A, although FDA does conduct surveillance and for-cause inspections of state-licensed pharmacies. Section 503A does not contain specific AE reporting requirements.

In 2013, Congress enacted new compounding legislation. This legislation, known as the Drug Quality and Security Act[35] (DQSA), added a new section 503B to the FD&C Act, which established a new category of compounders known as outsourcing facilities. Outsourcing facilities can compound and distribute drugs without receiving prescriptions for individually identified patients, but they are subject to, among other things, CGMP requirements, inspection by FDA according to a risk-based schedule, and reporting requirements for AEs associated with their products. Under section 503B(b)(5) of the FD&C Act, outsourcing facilities are required to submit reports of adverse drug experiences associated with the use of their compounded drug products. FDA receives AE reports associated with compounded products that are required to be submitted by outsourcing facilities, in addition to reports submitted voluntarily. FDA screens FAERS reports associated with compounded products to identify potential emerging safety and quality concerns. FDA staff collaborate across offices in the review of and follow up on the received reports.

5.6. Homeopathic Drug Products

Homeopathy is an alternative medical practice generally based on two main principles: (1) that a substance that causes symptoms in a healthy person can be used in diluted form to treat symptoms and illnesses (known as "like-cures-like"); and (2) the more diluted the substance, the more potent it is (known as the "law of infinitesimals").[36] There is a broad misconception that all homeopathic products

[34] https://www.fda.gov/drugs/guidancecomplianceregulatoryinformation/pharmacycompounding/default.htm.
[35] https://www.congress.gov/bill/113th-congress/house-bill/3204.
[36] The revised draft guidance for FDA staff and industry Drug Products Labeled as Homeopathic (October 2019) is available at https://www.fda.gov/drugs/guidancecomplianceregulatoryinformation/guidances/default.htm. When final, this guidance will represent the FDA's current thinking on this topic.

are highly diluted and generally composed of "natural" ingredients, and that they are therefore incapable of causing harm. However, as with all drugs, the safety of homeopathic drugs depends upon many factors, such as the product's intended use, dosage form, frequency of use, manufacturing quality, intended patient population, and the quantity and combination of ingredients.

The definition of drug contained in the FD&C Act includes articles recognized in the official United States Pharmacopeia, the official Homeopathic Pharmacopeia of the United States,[37] the official National Formulary, or any supplement to them. There are currently no homeopathic drug products approved by FDA. Unlike FDA-approved drugs, which have a known active ingredient that is readily identifiable, the active ingredients in a homeopathic product often exist as extracts from botanical sources, including those that pose potentially toxic effects such as belladonna and nux vomica. In addition, although the label of many homeopathic products indicates the strength of the active ingredient(s), expressed as a dilution, some do not.

Spontaneous reporting is the primary tool for the surveillance of homeopathic drugs. It is sometimes difficult for reporters to know that the subject of their report is a homeopathic drug. In addition, even when the ingredients of homeopathic products are labeled, details regarding product ingredients are often lacking in spontaneous reports, which limits the reviewer's ability to properly identify the product. For these reasons, it may be difficult for FDA to identify cases attributable to the homeopathic product. Any safety finding is particularly important and could warrant significant and prompt regulatory action against the manufacturer. In a revised draft guidance,[36] FDA describes how the Agency intends to prioritize enforcement and regulatory actions for homeopathic drug products, using a risk-based approach.

5.7. Combination Products

As set forth in 21 CFR Part 3, a combination product is a product composed of two or more different types of medical products (i.e., a combination of a drug, device, and/or biologic with one another).[38] The drugs, devices, and biologics included in combination products are referred to as *constituent parts* of the combination product. There are three potential modes of action for a combination product: drug, device, and biologic. Combination products typically have more than one identifiable mode of action. Reviewers consider each constituent part and the product as a whole when evaluating AE reports for combination products. A multidisciplinary process is followed to address identified safety issues.

5.8. Medication Errors

The surveillance of medication errors is challenging because of the lack of (1) regulations for applicants to report medication errors,[39] (2) a universally accepted definition for medication error,[40] and (3) detailed information in the ICSR to determine the cause of the error (or that an error occurred). FDA considers a medication error as any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of a health care provider, patient, or consumer. This is

[37] http://www.hpus.com/.
[38] The guidance for industry and FDA staff *Current Good Manufacturing Practice Requirements for Combination Products* is available at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.
[39] Medication errors may be reported in association with an AE.
[40] Wilmer A, Louie K, Dodek P, Wong H, Ayas N. Incidence of medication errors and adverse drug events in the ICU: a systematic review. *Qual Saf Health Care.* 2010;19:1.

based on the definition stated by the National Coordinating Council for Medication Error Reporting and Prevention.[41] The off-label use, misuse, abuse, and other deliberate or intentional uses of a drug product in a manner that is inconsistent with the FDA-required labeling is not generally considered a medication error.

FDA has multidisciplinary staff dedicated to minimizing medication errors related to the naming, labeling, packaging, and design for drugs and biologics. The Agency follows a rigorous preapproval review process for drugs and biologics that includes specific review activities to prevent medication errors. FDA reviews and accepts proposed proprietary names to minimize medication errors associated with product name confusion.[42,43] The Agency also reviews and provides feedback on proposed container labels, carton labeling, packaging, product design, prescribing information, Instructions For Use, and human factor studies to minimize or eliminate hazards contributing to medication errors. Review activities conducted in the preapproval period inform the approach for medication error monitoring once the product is approved for marketing. Similarly, the information learned from monitoring and analyzing medication errors reported postapproval is used to improve the preapproval review processes.

Throughout the postapproval period, FDA conducts systematic monitoring of medication errors. There are several reasons for this approach. First, the complete medication error safety profile of a product may be uncertain when the product is approved. Clinical studies performed in the preapproval phases involve a limited number of patients and health care providers. The studies may not use the labeling and packaging approved for marketing. Also, the studies may not involve the entire medication-use system, such as electronic prescribing, storage conditions, or barcode-assisted administration systems typically used in a real-world setting. Second, medication errors are associated with a significant public health burden.[44] Early detection through monitoring allows FDA to address a medication error before the product is more widely distributed. Third, prescribing practices and the marketplace are continually changing, due to advancements in technology, new therapeutic uses, approval of novel drugs and biologics, and the market entry of generic drugs and biosimilar products. Fourth, some products, such as OTC monograph products, may not undergo the product-specific preapproval review process, that prescription drugs and biologics are subject to prior to marketing.

FDA uses several sources of information for monitoring medication errors, including: FAERS and VAERS; partners and patient safety organizations; and PSR submissions. Reviewers routinely review ICSRs, carefully considering those that describe the potential for a medication error. All reports of medication error are examined, regardless of whether they result in an adverse event or whether the

[41] National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) definition and taxonomy for medication errors. Available at https://www.nccmerp.org/about-medication-errors.
[42] The guidance for industry *Contents of a Complete Submission for the Evaluation of Proprietary Names* is available at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.
[43] The draft guidance for industry *Best Practices in Developing Proprietary Names for Drugs* is available at https://www.fda.gov/drugs/guidancecomplianceregulatoryinformation/guidances/default.htm. When final, this guidance will represent the FDA's current thinking on this topic.
[44] In 2011, the Network for Excellence in Health Innovation reported that outpatient and inpatient preventable medication errors cost approximately $20 billion each year.

outcome is serious or nonserious. This approach is used to detect emerging safety issues in naming, labeling, packaging, and design.

FDA has established collaborative agreements with Federal and non-Federal partners and patient safety organizations to share medication error information. Under these collaborative agreements, FDA is alerted to possible emerging medication error issues. Medication errors are notably underreported, and collaborative agreements have proved to be an effective way to help monitor and address medication errors.

PSRs[45] submitted by applicants, particularly those in the Periodic Benefit-Risk Evaluation Report (PBRER)[46] format, are valuable in the overall monitoring of medication errors. The PBRER includes a cumulative tabulation of medication errors and a specific section that summarizes information on patterns of medication errors and potential medication errors, even when not associated with AEs. The availability of the PBRER for review by reviewers can be quite informative to medication error monitoring.

5.9. Specific Patient Populations

5.9.1. *Pregnant population*

During clinical development of most products, pregnant women have historically been excluded from clinical trials. Thus, prior to marketing there is limited information about a product's safety profile when used during pregnancy. FDA conducts drug safety surveillance on the use of products in the pregnant population much as it does for the use of products in the general population but has a specific focus on detecting product-induced fetal effects. The identification of a product's potential for adverse developmental outcomes, including teratogenicity,[47] is particularly important because product-induced adverse developmental outcomes are potentially preventable.

To optimize the detection and characterization of any adverse effects related to prenatal product exposure, FDA staff work collaboratively across the Agency and use all available postmarketing surveillance data sources. Data may be collected from a prospective pregnancy registry study as a postmarketing requirement or commitment. Data may also become available through AE reports submitted by patients or providers or through other pharmacovigilance strategies, including epidemiologic studies. Reviewers consider the strengths and limitations of each data source throughout the review to inform the assessment of adverse drug effects to the pregnant woman and the fetus.

A pregnancy exposure registry is a prospective observational study that actively collects information on medical product exposure during pregnancy and associated pregnancy outcomes. One advantage of registries is that they avoid bias that is inherent in studies relying on retrospective reporting. The

[45] See section 6.1.4, *Other information sources*.
[46] The guidance for industry *E2C(R2) Periodic Benefit Risk Evaluation Report (PBRER)* is available at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.
[47] In FDA reviewer guidance *Evaluating the Risks of Drug Exposure in Human Pregnancies*, the term *teratogen* is used to designate products with teratogenic potential at clinical doses used in humans; it is available at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

prospective collection of data from exposed women who enroll in the registry prior to the occurrence of an adverse outcome allows investigators to estimate the risks of a variety of adverse outcomes.[48] When well-conducted and sufficiently powered, findings from a registry-based study may inform whether a drug is a teratogen. However, because registries may enroll limited numbers of pregnant women, it may not be possible to detect a small increased risk of a birth defect that is frequently seen in the background populations. Moreover, while pregnancy registries are still the most common method used to collect pregnancy-related information in the postmarketing setting, registries are also subject to selection bias, confounding, and low enrollment, any of which can complicate the interpretation of the registry results.

Additional potential data sources for evaluating a specific drug safety signal associated with the use of a drug during pregnancy include observational studies, such as case-control studies, population-based surveillance and national registries, as well as electronic claims and health record databases. Such sources are often retrospective and usually designed to examine a specific hypothesis. These studies are typically larger than registry studies, particularly those that use electronic health care databases or national register data. Such studies often take advantage of linkages between multiple types of information sources including demographic, clinical, pharmacy, and vital statistics data. However, retrospective studies have limitations. They may rely on unvalidated diagnostic or procedure codes to identify study outcomes, or they may rely on electronic pharmacy data that cannot confirm whether the pregnant women who were dispensed the product actually took the product. Other potential limitations include errors in estimating gestational age and confounding due to the condition for which the pregnant woman received the treatment. Finally, many sources for retrospective studies limit study populations to only live birth populations. If the safety issue relates to an outcome incompatible with live birth (e.g., stillbirth, severe malformation not commonly resulting in live birth), results from these studies may lack generalizability at the very least, or potentially suffer from selection bias.

ICSRs provide yet another source of information that may be used to evaluate specific drug safety concerns in pregnancy. Although in rare circumstances a single ICSR can provide sufficient information necessary for making a reasonable inference about causality in the assessment of teratogenicity, a series of similar reports of a distinct abnormality or group of similar abnormalities can establish a strong association or signal the need for follow-up evaluations to assess the potential risk. Several well-established teratogens were first identified by a case report or case series.[49,50,51] There are several factors to consider when evaluating ICSRs reporting potential congenital anomalies. These include (1) the physical and chemical nature of the product; (2) the dose, duration, frequency, and route of exposure; (3) gestational timing; (4) concurrent products and comorbidities; (5) background prevalence of adverse pregnancy outcomes; (6) combined versus individual rates of birth defects; and (7) major versus minor birth defects. It is well known that data collected retrospectively may be subject to bias. When analyzing data on adverse outcomes following in utero exposure, it is important that reviewers evaluate prospective

[48] The guidance for industry *Establishing Pregnancy Exposure Registries* is available at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

[49] Mitchell AA. Adverse drug reactions in utero: perspectives on teratogens and strategies for the future. *Clin Pharmacol Ther.* 2011;89(6):781-783.

[50] Shepard TH. Agents that cause birth defects. *Yonsei Med J.* 1995;36(5):393-396.

[51] Goldberg JD, Golbus MS. The value of case reports in human teratology. *Am J Obstet Gynecol.* 1986;154(3):479-482.

reports, those in which information on the patient was collected after exposure but prior to knowledge of the pregnancy outcome, separately from retrospective reports, those in which the pregnancy outcome was known at the time of reporting.

5.9.2. *Pediatric Populations*

Safety information from adult human studies and animal models may provide preliminary information regarding the expected safety profile of a drug in pediatric populations, but safety information from administration of the drug to children is generally needed to evaluate fully the safety profile of a drug in children. It is well-recognized that there are age-specific changes in drug absorption, distribution, metabolism, and excretion that can affect both the dosing and safety of a drug in children. In addition, long-term follow-up studies, particularly for drugs used in infants or young children, may be needed to assess fully the long-term safety of a drug when used in children.

Congress passed legislation that has improved the availability of drugs and biological products approved for use in children. The Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA)[52] provide both incentives and requirements (respectively) for the collection of pediatric-specific safety and efficacy information. Under BPCA, FDA may issue a Written Request for pediatric studies for a drug that may provide health benefits in children. A Written Request may be issued for both approved and unapproved indications. Sponsors may decline to conduct the requested studies. Under PREA, a pediatric study can be required under certain circumstances. Product labeling is updated to reflect studies conducted under PREA (section 505B(g)) and BPCA (section 505A(i) and (j)).

Eighteen months after the date of a pediatric labeling change for the product, a cumulative safety summary analysis[53] of pediatric AE reports is conducted by a multidisciplinary team and referred to the Pediatric Advisory Committee (PAC) for external expert input. Members of the PAC review the analysis and can recommend additional actions for FDA consideration.

Importantly, BPCA and PREA do not apply to all products or applications for products used in the pediatric population, and the pediatric use of drugs that have not been studied in pediatric populations continues to occur. Reviewers conducting pharmacovigilance for products not studied in the pediatric population include an evaluation of use and considerations for unintentional overdose manifesting in exaggerated physiological effects.

When analyzing ICSRs for the pediatric population, it is often necessary to analyze reports in specific age groups. Chronic conditions may require long-term treatment and latent adverse drug effects may be different based on the age and stage of growth and development of the patient when the drug was initiated. Therefore, reviewers monitor reports for all latent adverse drug effects, including those

[52] BPCA, which amended the FD&C Act to add section 505A (21 U.S.C. 355a), was originally enacted in 2002 (Public Law 107-109, 115 Stat. 1408 (Jan 4, 2002)). PREA, which amended the FD&C Act to add section 505B (21 U.S.C. 355c), was originally enacted in 2003 (Public Law 108-155, 117 Stat. 1936 (Dec 3, 2003)). Both were permanently reauthorized in 2012 as part of the Food and Drug Administration Safety and Innovation Act (FDASIA).

[53] The analyses are prepared for the Pediatric Advisory Committee (PAC) according to internal standard procedures for pharmacovigilance review.

describing endocrine dysfunction and reproduction effects, neurodevelopmental outcomes, delayed growth, and delayed or accelerated puberty.

Reviewers are vigilant in screening for AE reports that describe accidental exposures of various etiologies (e.g., defeated or defective child-resistant packaging or improperly discarded products). They also screen for reports of overdose related to unique aspects of drug delivery and potential errors in preparing specific formulations (e.g., dilution error) for this population.

5.9.3. *Geriatric Population*

ICSRs that describe AEs in the geriatric patient population warrant special consideration by reviewers, because at the time of a product's approval, there is typically limited data on its effects in the geriatric population, and thus postmarketing experience is important.

Aging is associated with well-described changes in organ function (e.g., renal function) that affect the pharmacokinetics and therefore the safety profile of pharmaceuticals. In addition, the geriatric population experiences not only an increased frequency of chronic disease, but also an increased concurrent utilization of multiple medications (*polypharmacy*). This contributes to the potential for serious AEs, which are reported to occur in 5 to 10 percent of the general elderly population. When hospitalized due to a drug AE, this population experiences in-hospital mortality rates as high as 10 percent.[54,55,56]

Impaired renal function can contribute to drug toxicity, due to accumulation of parent drugs and of certain metabolites that preserve variable levels of activity despite biotransformation. With aging, the prevalence of chronic kidney disease increases because of both age-related natural loss of renal function and incident disease. In this context, serum creatinine may underestimate renal function primarily because of age-related loss of muscle mass, which is the site of origin of creatinine.

Estimation of glomerular filtration rate (GFR) using standardized formulas is a better way to define renal function, although most of the current formulas were originally validated in younger populations and can be relatively unprecise in the elderly.[57,58] This can lead some clinicians to assume "normal" renal function in older patients, when in fact the actual GFR reflects a substantial decline from normal adult levels. The most accurate method of measuring GFR is the 24-hour creatinine clearance, but the difficulty of collecting an accurate 24-hour urine sample is a major limitation in older persons. In

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[54] Kongkaew C, Noyce PR, Ashcroft DM. Hospital admissions associated with adverse drug reactions: a systematic review of prospective observational studies. *Ann Pharmacother*. 2008;42(7):1017-1025.
[55] Bouvy JC, De Bruin ML, Koopmanschap MA. Epidemiology of adverse drug reactions in Europe: a review of recent observational studies. *Drug Saf*. 2015;38(5):437-453.
[56] van der Hooft CS, Dieleman JP, Siemes C, et al. Adverse drug reaction-related hospitalisations: a population-based cohort study. *Pharmacoepidemiol Drug Saf*. 2008;17(4):365-371.
[57] Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med.* 2009;150(9):604-612.
[58]The draft guidance for industry *Pharmacokinetics in Patients with Impaired Renal Function — Study Design, Data Analysis, and Impact on Dosing and Labeling* is available at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm. When final, this guidance will represent the FDA's current thinking on this topic.

reviewing AE reports for products that are eliminated renally, it is prudent to consider the potential for unrecognized renal dysfunction in the setting of an exaggerated pharmacodynamic effect.

Polypharmacy and the potential for drug-drug interactions represent another important concern for the geriatric population. It has been reported that 40 percent of patients over age 65 take 5 or more drugs on a chronic basis.[59] The likelihood for hospital admission due to an AE is much higher for older individuals. In addition, some drug-drug interactions result in predictable changes in PD effects, PK effects, or unforeseen effects due to the appearance of a novel active metabolite. It follows that good pharmacovigilance for the geriatric population includes considerations for previously unrecognized drug-drug interactions leading to both predictable and novel AEs.

5.10. Misuse, Abuse, Addiction, and Overdose

Many products are subject to misuse, abuse, addiction, and overdose, including fatal overdose. For purposes of this document, the term *abuse* is defined as the intentional, non-therapeutic use of a drug product or substance, even once, to achieve a desirable psychological or physiological effect.[60] Abuse is not the same as *misuse*, which refers to the intentional therapeutic use of a drug product in an inappropriate way and specifically excludes the definition of abuse.[61] FDA reviewers consider *overdose* to be the administration of a quantity of product above the maximum recommended dose.

In evaluating reports of misuse and overdose, reviewers stratify them by intentionality wherever possible. Reviewers examine specific product information to better understand the role of specific product characteristics as risk factors for misuse and abuse, as appropriate. Products found to be associated with misuse or overdose are evaluated for the need for changes to the labeling (indications, instructions for administration, packaging).

Information used to evaluate drug product abuse can come from a variety of sources, including FAERS reports, national surveys, calls to poison control centers, surveys of individuals entering treatment or under assessment for substance use disorders, and national mortality data. Reviewers utilize all of these data sources, because each has its own unique strengths and limitations. In evaluating AE reports, reviewers may not have information describing how the person experiencing an event obtained the product. The most obvious way to obtain a product, whether for legitimate use or intended abuse, is for a person to be dispensed a prescription. However, AEs from abuse commonly occur in individuals who may *not* have been prescribed the product.

The evaluation of AEs that result from product misuse and abuse is challenging because (1) AEs related to misuse and abuse may occur outside the health care system and may not be reported to FDA; (2) there is substantial geographic variation in levels, trends, and routes of abuse for any given product; (3) key information (e.g., product, frequency, and route of abuse) can only be gathered from the individual abusing the drug and generally cannot be verified; and (4) many health professionals do not accurately

[59] Kantor ED, Rehm CD, Haas JS, et al. Trends in Prescription Drug Use Among Adults in the United States From 1999-2012. *JAMA*. 2015;314(17):1818–1830.
[60] The guidance for industry *Assessment of Abuse Potential of Drugs* is available at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.
[61] Ibid.

record or are unaware of misuse and/or abuse-related behavior. Despite these challenges, reviewers assess trends and potential harm from misuse and abuse during the screening process.

It is well known that prescription opioid analgesic drugs are associated with overdose, addiction, and death that can result from problems of inappropriate prescribing, misuse, and abuse. The recent HHS report, *Addressing Prescription Drug Abuse in the United States: Current Activities and Future Opportunities*,[62] discusses both the public health crisis and actions that can be taken to help address this serious epidemic. It is important to note that products other than opioids, including some not requiring a prescription, are also subject to the same problems highlighted in the HHS report. Although problems related to non-opioid products don't receive the same attention from academia or the media, reviewers need to keep them in mind when conducting drug safety surveillance.

5.11. Product Quality Issues

For purposes of this document, FDA considers product quality issues (PQIs) to be deviations from the established A/NDA or BLA specifications for the drug product such as identity, strength, purity, and other characteristics designed to ensure the required levels of product quality, safety, and effectiveness.

Reviewers monitor for PQIs, which may be reported to FDA when there is a concern about the product's quality, authenticity, performance, or safety. PQIs may be reported as physical product issues (e.g., friable tablet, discoloration) or manifestations of PQIs (e.g., product ineffective, disease progression). Reports describing PQIs are reviewed by FDA product quality experts. Considerations for the assessment of PQIs in FAERS include the assessments of trends over time by manufacturer, lot number, or national drug code (NDC).

Signals identified from FAERS suggestive of a PQI are evaluated by multiple FDA offices and in the context of other available data streams (e.g., Field Alert Reports; Biological Product Deviation Reports; manufacturing facility inspection data; product distribution; bioequivalence data; and recent chemistry, manufacturing, or control changes). These signals may lead to further investigation including inspections and product evaluations (e.g., chemical and microbial sample analysis).

6. Safety Signal Identification

For the purposes of this document, the term *signal identification* is broad in scope. It includes the activities of screening FAERS, VAERS, and the medical literature, as well as accessing other information sources, to identify potential safety signals. Identified signals are prioritized for more extensive evaluation.

6.1. Data Sources

Multiple strategies and tools are used to identify safety signals in both the FAERS and VAERS databases. Reviewers routinely screen ICSRs at the report level and also screen ICSRs in a cumulative manner. In addition, systematic, automated techniques are used routinely, which lend efficiency to screening the database. These approaches complement each other and are described in the sections that follow. The

[62] https://www.cdc.gov/drugoverdose/pdf/hhs_prescription_drug_abuse_report_09.2013.pdf.

use of multiple strategies in concert allows FDA to manage the increasing number of ICSRs in both the FAERS and VAERS databases, to efficiently identify potential safety signals, and to facilitate the prioritization of potential safety issues.

The typical frequency for screening each of the data sources discussed in the following subsections is presented as a summary table in section 6.2.

6.1.1. *FAERS and VAERS*

Individual ICSR screening

Screening of individual ICSRs in the AE database begins with selecting the product or the AE based upon considerations for risk that are discussed in section 4, *Risk-based approach to drug safety surveillance*. By using risk-based principles, reviewers use screening tools first to identify potential signals; a more rigorous review is conducted later in the course of report analysis.

The quality of information provided in the ICSRs is highly variable.[63] It is critical that an ICSR be of high quality for optimal evaluation of the relationship between the product and AE. The most useful ICSRs contain detailed descriptive information in the narrative section to describe the AE as it occurred in the patient. Using the information in the narrative and other sections of the ICSR, reviewers attempt to establish a temporal relationship between administration of the product and occurrence of the AE to determine if there is sufficient support for further evaluation of the potential safety signal. For further details on assessment of ICSRs for causal association, see section 7.1.3.

If an ICSR does not include sufficient information to assess the suspected causal relationship between the product and event, the reviewers may follow up with the applicant or the reporter to obtain additional information necessary for case assessment. Reviewers also seek to learn more information about the event and how it resolved. They attempt to get more information about the circumstances surrounding the AE and other possible contributory or confounding factors (e.g., other concurrent products and pertinent medical history). They may also attempt to obtain autopsy reports and results of any laboratory or diagnostic tests, which are added to the database.

Cumulative screening

Reviewers perform cumulative screening of the AE database to provide an aggregate, high-level summary of the reported postmarketing safety experience (e.g., by clinically relevant AE terms, serious outcomes, year of occurrence, or any demographic variable of interest) for the product under evaluation. Screening of cumulative AE reports from multiple sources (e.g., health care providers, consumers, the medical literature) and of both serious and nonserious outcomes is one approach to better understanding the postmarketing safety profile of products.

The strategy for cumulative ICSR screening of a product under evaluation can include analyses of the AE terms most frequently reported in (1) all reports, (2) reports with a serious outcome, (3) reports with AEs of interest, and (4) reports for a specific population (e.g., pregnancy or pediatric exposure and outcome). This screening strategy also includes a review of PSRs for new safety signals or concerns. The goal of

[63] Information on FAERS data limitations is available at https://www.fda.gov/drugs/guidancecomplianceregulatoryinformation/surveillance/adversedrugeffects/.

this risk-based surveillance process is to generate an overview of serious unlabeled AEs, known AEs reported in an unusual number, or other new potential safety concerns with the product. In the course of cumulative screening, the reviewer may identify one or more AE(s) that may cause the reviewer to read in detail all ICSRs for the AE(s).

Periodic, cumulative screening of ICSRs complements ongoing screening at the individual report level.

6.1.2. *Data Mining*

Data mining in the context of drug safety surveillance refers to the use of statistical or mathematical tools to discover patterns of associations or unexpected occurrences in large databases, such as FAERS and VAERS. It involves the systematic examination of reported AEs to provide information about the existence of an excess of AEs reported for a product relative to other products in the database (disproportionality). Results from data mining are considered hypothesis generating and do not, by themselves, demonstrate causal associations.

By applying data mining techniques, FDA may be able to identify unusual or unexpected product-event combinations that warrant further investigation. FDA reviewers use data mining to assess patterns, as well as identify particular AEs associated with drug-drug interactions.[64] Reviewers consider both sensitivity and precision in the chosen approach. Unexpectedly high reporting associations (e.g., the doubling of a particular product-event combination over a specified time interval) may generate a hypothesis that there may be an association between the particular AE and the product. However, the absence of disproportionality does not confirm the absence of a safety signal or negate a signal detected by other methods.

It is necessary to adjust signal thresholds to account for the severity of the AE, severity of the condition for which the product is being used, and a product's established safety profile. For example, a lower signaling threshold may be considered for serious AEs (e.g., progressive multifocal leukoencephalopathy) or for products for which less may be known about the safety profile. The products and AEs that may be appropriate for a lower signaling threshold are discussed in section 4, *Risk-based approach to drug safety surveillance*. Additionally, the database can be filtered by various characteristics (e.g., pediatric reports or serious outcomes) to identify potential signals.

6.1.3. *Medical Literature*

FDA reviewers routinely screen the medical literature in an effort to identify emerging safety signals that are not submitted as ICSRs to FDA. Screening is accomplished by searching the medical literature by product or by AE. The principles underlying how reviewers select products and AEs for screening are discussed in section 4, *Risk-based approach to drug safety surveillance*.

Reviewers supplement their screening of published AE case reports with additional data sources, such as studies completed by academic institutions or other researchers outside of FDA, studies performed by

[64] The guidance for industry *Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment* discusses and provides recommendations on the use of data mining and is available at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

other Government agencies and referred to FDA for comment, and other studies that FDA becomes aware of. These may be presented in peer-reviewed or online journals or as abstracts at conferences. The information is made available in a variety of forms, including case reports of clinical AEs and health care professionals' interpretations of postmarketing safety data. Reviewers also have access to findings from patient registry studies, observational and pharmacoepidemiologic studies, meta-analyses, and randomized controlled clinical trials.

6.1.4. *Other Information Sources*

In addition to systematically screening and data mining the FAERS and VAERS databases and monitoring the medical literature, reviewers make use of other sources of information that can give rise to signals. Safety signals can arise during studies conducted as part of product development, such as animal studies, in vitro studies, or an imbalance in safety findings in clinical trials that was not considered an adverse drug reaction at the time of approval. During the preapproval review process, potential signals that are identified by the clinical reviewer, especially those arising in Phase II and Phase III clinical trials, lead to multidisciplinary discussions to determine what, if any, postmarketing activities are needed.

Application holders submit required PSRs to FDA on a recurring basis for review.[65] PSRs provide summary information directly from the applicant, which may include clinical and nonclinical study reports and the applicant's assessment of the marketed product's benefit-risk profile. PSRs may supplement the spontaneous reports available to reviewers for identifying potential safety signals and learning about potential changes in the benefit-risk profile for marketed products. In addition to the PSRs specified in FDA regulation, FDA accepts PSRs prepared in accordance with ICH E2C guidelines.[66] The PSRs submitted using an ICH format provide additional data and information to that required by FDA regulation, which can materially inform the safety review process. In reviewing PSRs, reviewers pay particular attention to products with recently approved new indications or worldwide safety data with concerning findings that might indicate an emerging safety signal.

REMS assessments can contain useful information regarding important identified risk(s). FDA can require a REMS when FDA determines that a risk evaluation and mitigation strategy beyond approved professional labeling is necessary to ensure that the benefits of the drug outweigh its risks. REMS generally must include a timetable for submission of assessments of the REMS.[67] The timetable must include an assessment by the dates that are 18 months and 3 years after the REMS is initially approved

[65] FDA's postmarketing safety reporting regulations require applicants to submit PSRs in the form of a periodic adverse drug experience report (PADER) (for drugs) or a periodic adverse experience report (PAER) (for biologics) (21 CFR 314.80(c)(2) and 600.80(c)(2)).

[66] With an approved waiver (under 21 CFR 314.90(b) and 600.90(b)), the Periodic Safety Update Report (PSUR) and the PBRER are accepted PSR formats.

[67] New Drug Applications (NDAs) and Biologics License Applications (BLAs) must include a timetable for submission of assessments. Abbreviated new Drug Applications (ANDAs) are not subject to the requirement for a timetable for submission of assessments (Section 505-1(i)), but FDA can require any application holder, including ANDA applicants, to submit REMS assessments under Section 505-1(g)(2)(C). The draft guidance for industry *Format and Content of a REMS Document* is available at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm. When final, this guidance will represent the FDA's current thinking on this topic.

and an assessment in the 7th year after the REMS is approved or at another frequency specified in the REMS. REMS are discussed in greater detail in a subsection of section 9, *Actions*.

A risk management plan (RMP) is a document prepared by the applicant that describes the product's safety profile (e.g., important identified risks, important potential risks, and important missing information), planned pharmacovigilance and studies for these safety concerns, and how known risks associated with the product will be managed. U.S. regulations do not require submission of RMPs as a condition of approval; however, some other regulatory authorities do. Applicants may submit an RMP prepared for another authority to FDA, in which case it may serve as an additional source of safety information.

A variety of additional information sources for signals are generally received on an ad hoc basis. They include applicant submissions of supplements to make a postapproval safety-related labeling change(s). Signals may also be identified following receipt of a citizen petition[68] requesting that FDA take action based on factual or legal grounds. FDA has ongoing communications with international regulators, which may lead to identification of signals. In addition, FDA may become aware of drug safety issues through media inquiries or reports.

6.2. Frequency and Extent of Screening

The extent and frequency for screening the FDA AE databases and the medical literature varies with the product type. Products are grouped into three categories[69] for ease of reference; a summary for screening the FDA AE databases by product category appears below in the Table and is described in some detail in the paragraphs that follow.

Category A

Generally, on a weekly basis, reviewers screen newly received ICSRs[70] for products in the first 3 years following approval. These products include (1) NMEs; (2) originator biological products; (3) biosimilars; and (4) products without NME designation but having newly approved dosage form(s), newly approved indication(s), extension into new patient populations, complex PK or PD characteristics, or complex compositions or manufacturing processes.

Additionally, reviewers perform screening on a periodic basis of cumulative data in the FDA AE databases for these products, including data mining. In many cases, these screenings are scheduled to coincide with PSR receipt to leverage resources and optimize efficiencies. PSR submissions, which contain the manufacturer's analysis on a cumulative basis, inform the overall review. Products in this category that are beyond 3 years postapproval are screened as described for category C.

Category B

[68] 21 CFR 10.30, accessible at: https://www.ecfr.gov/cgi-bin/retrieveECFR?gp=1&SID=bd7d8fe119073e6a690a878c505a1af2&ty=HTML&h=L&mc=true&n=pt21.1.10&r=PART.

[69] The description here describes CDER's grouping of products into categories. CBER follows similar principles but does not group products into categories.

[70] Reviewers, generally, additionally screen the medical literature on a weekly basis.

Reviewers generally screen on a weekly basis newly received ICSRs and the medical literature for homeopathic and compounded products.

Category C

Reviewers generally screen the database weekly for newly received ICSRs that report AEs of interest for (1) any product in category A that is beyond 3 years postapproval, (2) OTC products, and (3) any product not in category A or B. In addition, reviewers generally perform data mining at least yearly for category C products.

Table: General Screening Frequency

Screening Category	FDA Adverse Event databases
A	Weekly for newly received ICSRs
	At intervals coinciding with PSR receipt for all ICSRs since approval, including data mining
B	Weekly for newly received ICSRs
C	Weekly for newly received ICSRs reporting AEs of interest
	Yearly (at minimum) data mining of all ICSRs since approval

A - Up to 3 years postapproval: NMEs; originator biological products; biosimilars; and products without NME designation but having newly approved dosage form(s), newly approved indication(s), extension into new patient populations, complex PK or PD characteristics, or complex compositions or manufacturing processes.

B - Homeopathic and compounded products.

C - Products in category A beyond 3 years postapproval. OTC products. Any product not in category A or B.

6.3. Signal Prioritization

Identified signals are prioritized both within and across products. Prioritization is made based upon the nature of the AE, the seriousness of the outcome, the impact on the individual, and the impact on public health. When new information becomes available that may change the benefit-risk profile of a product, the signals are reevaluated and reprioritized.

In examining the AE, reviewers determine whether the signal is a serious AE (i.e., one that involves patient outcomes of death, life-threatening AEs, inpatient or prolonged hospitalization, persistent or significant disability/incapacity, congenital anomaly, or other serious important medical events). Reviewers also consider the severity of the AE relative to the disease being treated in the individual patient, as well as the effects of the AE on the individual patient in the absence of intervention. In

addition, reviewers consider the impact of the AE on the health of the overall treatment patient population and the broader impact on public health. Signal prioritization allows for effective signal management, including evaluation, timelines, decisions, and regulatory actions and plans.

7. Signal Evaluation and Documentation

A multidisciplinary team conducts an integrated, comprehensive evaluation of the prioritized signal to determine whether and what regulatory action(s) are indicated. The team integrates the cumulative data gathered from all available sources, which includes ICSRs submitted to FAERS and VAERS, medical literature case reports, product utilization data, reporting ratios, and epidemiologic assessments.

7.1. FAERS, VAERS, and the Medical Literature

7.1.1. *ICSR Retrieval*

In preparing to retrieve ICSRs, the reviewer considers the signal to be evaluated and determines whether to cast a broad search (sensitivity) or a narrow search (specificity). For example, a broad search can retrieve all ICSRs for a specific product or product class, while a narrow search can be constructed to retrieve ICSRs for a specific product by a specific manufacturer and for a particular time period. A broad search is most useful for exploratory searches of the database or for evaluating a signal with novel features. A narrower search is more appropriate for examining a particular aspect of a known risk. Best practices for reviewers in searching FAERS are covered in an internal document and include considerations for selecting product and AE terms to optimize the sensitivity and specificity of search results.

7.1.2. *Case Definition*

A case definition is a set of uniformly applied criteria for determining whether a person should be identified as having a particular disease, injury, or other health condition. It is developed by a multidisciplinary team based on information from the medical literature and current expert clinical practice guidelines. A case definition comprises a specific combination of signs, symptoms, and test results. As a conservative approach, a report that has been corroborated by a physician or other health care provider with relevant training is generally deemed to meet the case definition even if all of the diagnostic criteria are not explicitly included. Depending on the complexity of the diagnosis and the setting in which it was made, reviewers should discuss in their review their rationale for including or excluding such reports in a case series.

The use of a case definition in the comprehensive evaluation of a postmarketing safety signal is often necessary when the signal is generated from spontaneous AE reports. Reviewers evaluate individual ICSRs for potential inclusion in a set of similar cases (section 7.1.4, *Case series*) by using, as a point of reference, a case definition for the event. A case definition consists of pre-specified criteria for determining whether an individual report belongs in the case series. When available, it is preferable that reviewers use an existing case definition. However, the combined characteristics of the particular AE and the particular product may require modification of the existing case definition. It is important to note that the use of a case definition does not involve a causality assessment or establish criteria for the management of patients, nor does it require evidence of exposure to the product.

7.1.3. *Assessment of ICSRs for Causal Association*

Postmarketing AEs are reported from a variety of sources, including commercial marketing experience, postmarketing clinical studies, medical literature, and direct reports from health care professionals and consumers. The process of assessing potential causal associations between an AE and a product presents many challenges to reviewers and other staff involved in safety surveillance. Although a variety of methods has been developed to standardize the causal association assessment process, none has been validated.[71,72,73] Causal association assessments are conducted at the ICSR (report) level as well as the overall product-AE level. Considerations for causal assessment at the ICSR level are described below, while section 8 describes considerations at the product-AE level.

When assessing an ICSR for causal association, reviewers are focused on evaluating the relatedness of the AE to the product taken by the individual patient described in the ICSR. They evaluate a number of features, which can be divided into five broad categories: (1) chronologic data (e.g., plausible temporal sequence, dechallenge, rechallenge),[74] (2) precedents (e.g., similar AEs with the same product or related products), (3) biological or pharmacological plausibility (e.g., toxic drug concentration in body fluid, occurrence of a recognized pharmacodynamic phenomenon), (4) information quality, and (5) alternative etiologies (e.g., concurrent diseases or conditions, concomitant medications). Some of those features are also considered during the causal assessment at the product-AE level (e.g., precedents, biological or pharmacological plausibility), as outlined in section 8.

Once the aforementioned ICSR features have been evaluated, reviewers categorize the ICSR using a binary categorical system (i.e., related or unrelated). For example, a case with a plausible temporal relationship and an absence of factors with a contributory role would be considered a related case. On the other hand, cases without a temporal relationship and describing alternative etiologies with a contributory or confounding role would be considered unrelated.

Information from spontaneous reporting systems generally cannot provide definitive answers regarding causal associations between a product and an AE. However, a well-documented case of a rare AE,[75] one that is usually drug-related, or a well-documented report of positive rechallenge can be sufficient to strongly suggest or even establish a causal association.

7.1.4. *Case Series*

After retrieving the cases, applying the case definition, and accounting for duplicate reports, reviewers assess the ICSRs for causality and assemble a case series built upon those meeting all criteria. The

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[71] Meyboom R, Hekster Y, Egberts A, et al. Causal or casual? The role of causality assessment in pharmacovigilance. *Drug Saf*. 1997;17(6):374-389.

[72] Agbabiaka T, Savovic J, Ernst E. Methods for causality assessment of adverse drug reactions: a systematic review. *Drug Saf*. 2008;31(1):21-37.

[73] The guidance for industry *Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment* is available at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

[74] *Dechallenge* is the withdrawal of a suspect product from a patient's therapeutic regimen; *rechallenge* is the reintroduction of a product suspected of having caused an AE following partial or complete disappearance of the AE after withdrawal of the suspect product.

[75] For example, cases of progressive multifocal leukoencephalopathy in psoriasis patients treated with efalizumab. Kothary N, Diak IL, Brinker A, et al. Progressive multifocal leukoencephalopathy associated with efalizumab use in psoriasis patients. *J Am Acad Dermatol*. 2011;65(3):546-551.

review document includes a summary of the considerations or rationale for inclusion of the ICSRs in the case series, as well as descriptive clinical information that characterizes the case series, such as patterns and trends of the AE across the cases. In addition, summaries for select ICSRs that are the most informative or that otherwise best represent the cases in the series are discussed in some detail.

7.2. Product Utilization

Product utilization analyses are conducted to quantify and evaluate the use of medical products in the U.S. population. These analyses inform FDA's regulatory decision making about how to address a drug safety signal. Depending on the data sources used, these analyses can provide important information about patient demographics, prescriber specialty, diagnoses and procedures associated with the patient visit, directions for use, prescribed dosing, dosage form or route of administration, duration of product use, products taken concurrently, and use during pregnancy.

Principles of pharmacy practice, health care delivery, and pharmacoepidemiology are used to evaluate and interpret these data alongside electronic health care data to describe and characterize product utilization and treatment patterns in the United States. Several types of proprietary product utilization data are available to FDA, including sales distribution data, outpatient prescription- and patient-level data, hospital discharge billing data, office physician survey data, and longitudinal health care claims-level data. Data obtained from product manufacturers may also be used in the assessment.

The particular data source(s) and methods to be used for each product utilization analysis are selected based upon the characteristics of the signal (e.g., AE, specific patient populations, setting of care) as well as utilization patterns. Because U.S. national utilization data across all settings of care is not available,[76] multiple data streams are often necessary to project national estimates of product usage. Patient- and prescription-level product utilization analyses are often conducted for the primary setting(s) of care in which the product is dispensed or administered to characterize the patient population of interest or the primary setting of care associated with the AE or other safety issue. These analyses provide information on the extent of patient exposure, as well as a description of patient characteristics and patterns of use. Overall, product utilization analyses can provide context for pharmacovigilance activities and define the landscape of real-world use.

7.3. Reporting Ratios

When a signal is identified from FAERS or VAERS, examining the reporting ratio (sometimes called a reporting rate) informs signal evaluation. Reporting ratios, although not incidence rates, can be used to provide context and generate hypotheses. Reporting ratios are based on drug utilization, which may be measured in units of patients exposed, prescriptions dispensed, or amount of drug sold at wholesale. The numerator is derived from counts of ICSRs associated with the drug of interest that were reported to FAERS or VAERS during a specified time period. In calculating the reporting ratio, FDA typically uses the number of dispensed prescriptions as the denominator, where it serves as a surrogate measure of drug exposure in the population over a specific time period. The number of dispensed prescriptions is

[76] Although national utilization data across all settings of care is available in countries with a single-payer system, those data are not generalizable to the U.S. population.

estimated from proprietary drug utilization databases, which are described above in section 7.2, *Product utilization*.

Although reporting ratios are useful in informing signal evaluation, they have limitations. The numerator (representing the number of ICSRs) and the denominator (derived from product use data) are obtained from different data sources. There are additional factors that introduce uncertainty. For example, underreporting of AEs is common, and product use data are based on national estimates, not actual counts. If indicated and feasible, these calculations are followed by formal inferential analyses using rigorous postmarketing studies in population- or disease-based data sources. Reporting ratios are not considered in isolation; reviewers must take into account all available data and the strength of such data.

Reporting ratios can be calculated prior to building a case series (i.e., prior to applying the case definition and assessing causality); in this situation the reporting ratio is based on total report counts for the drug-AE pair of interest. The reporting ratio can also be calculated after building the case series, in which case duplicate reports and other factors are accounted for (section 7.1.4, *Case series*). Whether calculated before or after building the case series, reporting ratios are only crude estimates. They are useful for providing context and generating hypotheses to the extent that inherent limitations from each data source are addressed appropriately (e.g., both numerator and denominator are aligned by date, time period, indication for use, setting of care, and reporting rule considerations).

7.4. Epidemiologic Assessments

Epidemiologic assessments are often an integral part of the signal evaluation process. Preliminarily, a thorough review of the medical literature is performed to determine whether the signal has been previously identified or evaluated by other researchers and what unanswered questions might remain. In addition, the applicant, a multidisciplinary FDA team, or both may reassess the available clinical trial data for the drug (or drug class) during the postmarketing period.

Through the Sentinel Initiative,[77] FDA accesses information from large electronic health care databases, such as electronic health records, insurance claims data, and registries. These health care databases are made available by a diverse group of data partners through a distributed data system that enables FDA to actively gather information (active surveillance) about the safety of marketed products. Exploratory analyses are conducted to characterize health outcomes, examine medical product use, and explore the feasibility of conducting more detailed evaluations. Using automated design tools, as well as statistical methods that control for confounding, FDA may conduct additional analyses to build on prior work and formally evaluate medical product-outcome associations.

8. Causal Association Between Product and AE

The determination of whether there is a causal association between a product and an AE is based on the strength of evidence from the totality of data for the product under review. Causal association assessments made at the ICSR level (section 7.1.3) reflect the individual patient who experienced the AE. Aggregate data evaluation takes into account several different considerations, such as the number of well-

[77] In-depth information about the Sentinel program is available at https://www.fda.gov/safety/fdas-sentinel-initiative/fdas-sentinel-initiative-background.

documented cases in the case series, the consistency of the data, and the presence of features used for causal association assessment, especially biological and pharmacological plausibility. In addition, precedents of similar AEs with the same product or related products (e.g., drug class) are taken into consideration.

The evaluation of biological and pharmacologic plausibility is an important element of causal association assessment, and it is necessary to perform further evaluation when the plausibility is unclear or lacking. FDA performs such assessments to gain a better understanding of the mechanisms underlying drug or biological product toxicity, as well as insights into the links between a drug's chemical structure and its potential to induce AEs. Computational tools and predictive modeling related to a drug's mechanism of action or chemical structure-activity relationships can be used to bolster the causal association evidence between a drug and an AE, particularly when the number of reported cases is limited. PK or PD modeling and other pharmacologic or toxicologic evaluations may provide additional insight into plausibility, including class effect.

In addition to the aforementioned assessments, determination of causal association between product and AE may require a comprehensive review of all other available information, including the medical literature and premarket development programs (e.g., clinical studies, trials, and toxicological data). Other data, such as product utilization, reporting ratios (or rates), results from epidemiologic studies, and postmarketing studies or trials add to the strength of evidence.

9. Actions

Following the comprehensive review, the multidisciplinary team may determine that subsequent actions are necessary. Potential actions include requiring the applicant to change the product labeling, issuing a drug safety communication, gathering additional data through requiring a postmarketing study or trial with the aim of better characterizing the risk, and requiring a new REMS or modifying an approved REMS to better mitigate the risk.

If insufficient evidence exists to support a causal association between the drug and AE, the AE can be considered an AE of interest for continued close monitoring. Regardless of regulatory action taken, FDA continues to monitor for new safety information that may change the determination.

9.1. Product Labeling Changes

FDA-approved product labeling for health care professionals is the primary source of information about a product's safety and efficacy; the labeling summarizes the essential scientific information needed for the safe and effective use of the product.

FDA is authorized to require drug and biological product application holders to make safety-related labeling changes based on new safety information that becomes available after approval of the drug or

biological product.[78] FDA guidance documents describe the Agency approaches to such labeling changes, including where in the labeling the changes are to appear.[79,80,81]

9.2. Safety Communications

FDA develops and disseminates information to the public about important drug safety issues, including emerging drug safety information. Timely communication of important drug safety information provides health care professionals, patients, consumers, and other interested persons with access to the most current information concerning the potential risks and benefits of a marketed drug, helping them to make more informed treatment choices. A Drug Safety Communication (DSC) is a specific tool used by FDA to communicate important new and emerging safety information about marketed products to health care professionals and to patients.[82]

FDA issues DSCs after considering whether the communicated information can aid prescribing decisions, affect a patient's decision to use the drug, or whether actions can be taken to avoid, prevent, or minimize harm. DSCs highlight emerging safety issues that pose potentially serious or life-threatening risks or AEs. They may relate to previously unknown interactions, a potential medication error, or updated information about a known AE. DSCs generally convey information regarding:

- The safety issue and the nature of the risk being communicated.
- The approved indication or use of the product.
- The established benefit or benefits of the product being discussed.
- Recommended actions for health care professionals and patients, when appropriate.
- A summary of the data reviewed or being reviewed by FDA.

In addition to FDA-issued communications, applicants may be requested or required by FDA to issue a Dear Health Care Provider letter, for example, to disseminate information regarding a significant hazard to health, to announce important changes in prescribing information, or to emphasize corrections to prescription drug advertising or prescribing information.

9.3. Postmarketing Studies and Trials

FDA is authorized to require that applicants holding approved NDAs and BLAs conduct additional studies or clinical trials under certain circumstances.[83] Under section 505(o)(3)(D)(i), before requiring a

[78] Section 505(o)(4) of the FD&C Act.
[79] The guidance for industry *Safety Labeling Changes — Implementation of Section 505(o)(4) of the FD&C Act* is available at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.
[80] The guidance for industry *Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products — Content and Format* is available at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.
[81] The guidance for industry *Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products — Content and Format* is available at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.
[82] The guidance for industry *Drug Safety Information – FDA's Communication to the Public* is available at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.
[83] See, e.g., the guidance for industry *Postmarketing Studies and Clinical Trials — Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act* is available at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

postmarketing study, FDA must find that AE reporting under section 505(k)(1) of the FD&C Act and the active postmarket risk identification and analysis sytem[84] established under section 505(k)(3) of the Act will not be sufficient to meet the purposes described in section 505(o)(3)(B). Under section 505(o)(3)(D)(ii), before requiring a postmarketing clinical trial, FDA must find that a postmarketing study will not be sufficient to meet the purposes described in section 505(o)(3)(B).

9.4. Enhanced Pharmacovigilance

In an effort to enhance FDA's ability to perform safety surveillance of AEs of interest, FDA may request that the applicant:

- Use a targeted data collection tool to gather detailed case information specific to the product and AE of interest.
- Expeditiously submit reports of labeled AEs of interest beyond minimum reporting requirements.
- Summarize and assess AEs of interest at a frequency defined by FDA (e.g., in PSRs or in some other form).

9.5. Web Posting of Potential Safety Signals

In accordance with statutory requirements and established policies and procedures, FDA routinely posts potential signals identified from available data sources. Potential signals of serious risks or new safety information that were identified from FAERS, or for which FAERS data were contributory, are posted to the FDA internet website. [85,86]

A new report is made available each quarter. Information from previous quarters is updated on the website and remains available until an FDA regulatory action has been taken or FDA determines that no regulatory action may be required. FDA may determine, for products that may be associated with the risk, that one or more of the following actions is required: modifying the product labeling, gathering additional data to characterize the risk, a REMS or a modification to a REMS is necessary to ensure the benefits of the drug outweigh the risks, or suspending or withdrawing marketing approval. After FDA has taken a regulatory action for each issue on a quarterly report or determined that no regulatory action is required, no further updates are made, and the quarterly report is archived.

In addition to the quarterly posting, a separate website posting includes signals evaluated under the Sentinel program.[87] The information posted to the Sentinel website is provided as part of FDA's

[84] Information about the system, known as ARIA, is available at https://www.sentinelinitiative.org/active-risk-identification-and-analysis-aria.
[85] MAPP available at https://www.fda.gov/downloads/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cder/manualofpoliciesprocedures/ucm248882.pdf.
[86] See *Potential Signals of Serious Risks/New Safety Information Identified from the FDA Adverse Event Reporting System (FAERS)* at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/ucm082196.htm.
[87] In-depth information about the Sentinel program is available at https://www.sentinelinitiative.org/.

commitment to make knowledge acquired from the Sentinel system available in the public domain as soon as possible.

For each of these postings, the appearance of a product on the listing does not mean that FDA has concluded that the product is causally associated with the AE. It means that FDA has identified a potential safety signal for further evaluation, unless FDA has specifically stated that it has concluded that there is a causal association between the product and the AE, by noting, for example, in the posting that a label update has been made reflecting causality.

9.6. Risk Evaluation and Mitigation Strategies

FDAAA amended the FD&C Act to authorize[88] FDA to require a REMS when FDA determines that a REMS is necessary to ensure that the benefits of a drug[89] outweigh its risks. A REMS therefore provides additional risk mitigation beyond product labeling and can provide safe access for patients to products (approved under an NDA, BLA, or ANDA) with known serious risks that would otherwise be unavailable. A guidance for industry clarifies how FDA applies the factors for determining when a REMS is necessary to ensure the benefits of the drug outweigh the risks.[90]

Once the need for a REMS is determined, FDA considers the intended goal(s) of the REMS and specific strategies to meet the goals. A REMS can include a Medication Guide,[91,92] a communication plan, elements to assure safe use (ETASU), an implementation system, and a timetable for assessment of the REMS. A communication plan to health care providers may be required if FDA determines that the plan may support implementation of the REMS, to disseminate information to health care providers regarding REMS requirements, or to explain certain safety protocols, such as medical monitoring through periodic laboratory tests.

FDA can require ETASU as part of a REMS to mitigate a specific serious risk listed in the labeling of a drug if, in the absence of a REMS with ETASU, the drug would otherwise not be approved or would be withdrawn. A REMS that includes ETASU may comprise, for example, requirements that health care providers who prescribe the drug have particular training or experience, that patients using the drug be monitored, or that the drug be dispensed to patients with evidence or other documentation of safe use conditions.

A REMS may be required as a condition of the approval of a new product or for an approved product when new safety information becomes available that indicates that such a strategy is necessary to ensure

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[88] The requirements for REMS are found in section 505-1 of the FD&C Act.

[89] A REMS can be required for prescription drugs, whether brand or generic (i.e., products approved under an NDA, BLA, or ANDA).

[90] The guidance for industry *REMS: FDA's Application of Statutory Factors in Determining When a REMS Is Necessary* is available at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

[91] Federal regulations authorize FDA to require a Medication Guide as a part of drug product labeling under certain circumstances (21 CFR 208). Additionally, section 505-1 of the FD&C Act authorizes FDA to require a Medication Guide as an element of a REMS. FDA may decide that the Medication guide should be required as labeling (but not as part of a REMS).

[92] The guidance for industry *Medication Guides — Distribution Requirements and Inclusion in Risk Evaluation and Mitigation Strategies (REMS)* is available at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

the drug's benefits continue to outweigh the risks. New safety information is defined as a serious risk associated with the use of the product that FDA has become aware of since the product was approved, since a REMS was required, or since the last assessment of the REMS.[93] Applicants are required to periodically assess their REMS and submit such assessments to FDA as to whether the programs are meeting their goals or should be modified. Applicants work with FDA to modify their REMS throughout the life cycle of the product as new information becomes available. FDA reviews all REMS assessments. Assessments of approved REMS provide a valuable source of information for reviewers as well as a safety surveillance tool to ensure that a product is used safely.

10. Exploring New Approaches

To enhance its capabilities in promoting product safety to protect and improve public health, FDA continues to explore new approaches to drug safety surveillance. Likewise, through the establishment of partnerships and contractual arrangements, FDA aims to support and further develop new data systems, new surveillance infrastructure, and new methodological tools to complement its existing resources.

11. Acronyms Used

AE	adverse event
ANDA	abbreviated new drug application
ARIA	active risk identification and analysis system
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
CBER	Center for Biologics Evaluation and Research
CDC	Centers for Disease Control and Prevention
CDER	Center for Drug Evaluation and Research
CGMP	current good manufacturing practice
DQSA	Drug Quality and Security Act
ETASU	element to assure safe use
FAERS	FDA Adverse Event Reporting System
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act

[93] Section 505-1(b)(3) of the FD&C Act.

1096	FD&C Act	Federal Food, Drug, and Cosmetic Act
1097	GFR	glomerular filtration rate
1098	ICH	International Council for Harmonisation
1099	ICSR	individual case safety report
1100	MAPP	Manual of Policies and Procedures
1101	NCVIA	National Childhood Vaccine Injury Act
1102	NDA	new drug application
1103	NDC	national drug code
1104	NME	new molecular entity
1105	OTC	over the counter
1106	PAC	Pediatric Advisory Committee
1107	PBRER	Periodic Benefit-Risk Evaluation Report
1108	PD	pharmacodynamic
1109	PHS Act	Public Health Service Act
1110	PK	pharmacokinetic
1111	PMR	postmarketing requirement
1112	PQI	product quality issue
1113	PREA	Pediatric Research Equity Act
1114	PSR	periodic safety report
1115	REMS	Risk Evaluation and Mitigation Strategy
1116	RMP	risk management plan
1117	SOPP	Manual of Standard Operating Procedures and Policies
1118	VAERS	Vaccine Adverse Event Reporting System