

Pharmacovigilance: reporting requirements throughout a product's lifecycle

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Abstract: Comprehensive methods for evaluating safety are needed to objectively assess the full risk profile of a medication. The confidence of the prescribing provider in the safety and effectiveness of pharmaceuticals is extremely important. Pharmacovigilance is a key component of drug safety regulatory processes and is paramount for ensuring the safety profile of medications used to treat patients. All participants in the healthcare system, including healthcare providers and consumers, should understand and meaningfully engage in the pharmacovigilance process; healthcare providers should integrate pharmacovigilance into everyday practice, inviting feedback from patients. This narrative review aims to give an overview of the main topics underlying pharmacovigilance and drug safety in pharmaceutical research phase after the authorization of a drug in the United States. The US Food and Drug Administration guidance and post-approval regulatory actions are considered from an industry perspective.

Plain language summary

Regulatory processes that ensure the safety of drugs is monitored

Government agencies regulate the safe use of medicinal products. By determining and enforcing pharmacovigilance, the monitoring of drugs for potential risks, they safeguard the welfare of consumers of medicines. Comprehensive, documented methods for evaluating the safety of a drug during its development and its subsequent use allow identification of any risks associated with the drug's use throughout its lifetime. The comprehensive identification of safety issues associated with a drug is improved when all parties involved in the development and use of drugs participate in the pharmacovigilance process. For example, clinicians should regularly ask their patients if they are experiencing any issues with their treatment, and patients should be encouraged to report problems they encounter with a particular medication to their healthcare provider. This narrative review provides an overview of the main topics underlying pharmacovigilance and drug safety after approval of a drug in the United States. Guidelines and actions from the US Food and Drug Administration are considered from an industry perspective.

Keywords: adverse events, adverse drug effects, clinical trials, drug tolerability, pharmacovigilance, postmarketing, regulatory, safety

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Introduction

Pharmacovigilance is the detection, monitoring, understanding, and prevention of adverse events (AEs) for a medicine.¹ Evaluation of a drug's safety begins in preclinical development, continues

through the drug's clinical trials, and extends past the product's approval into the postmarketing setting. While the assessment of safety in clinical trials provides insight to AEs that may occur in the indicated population, these studies are limited by their

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study duration and pre-defined patient population, which represents only a subset of the real-world population that may be eligible to use the drug once approved. Therefore, it is likely that potential safety concerns may be identified in the real-world setting that have not arisen during clinical trial evaluation. Postmarketing surveillance relies on pharmacovigilance to ensure that safety events related to the use of a drug throughout its lifetime are collected, evaluated, and acted upon as necessary to ensure the ongoing safe use of medicines.¹

Postmarketing surveillance of a drug, which may include post-approval surveillance studies (PASSs), facilitate continued risk management by identification of safety signals not identified during clinical development.¹ Although regulatory agencies and drug manufacturers play an integral role in the collection and reporting of drug safety, ultimately it is the participants in the healthcare system, namely healthcare providers (HCPs) and consumers, who provide the necessary inputs for pharmacovigilance monitoring and surveillance programs. Thus, HCPs and consumers should understand and meaningfully engage in the pharmacovigilance process to support the safe use of medicines. The foundation for drug safety data collection and reporting lies in federal regulations and guidelines, and basic knowledge of these processes is needed to understand postmarketing safety and regulatory actions. In this narrative review, we describe the high-level processes of pharmacovigilance activities and their impact on regulatory actions in the United States, including medicinal product label changes.

Definition of pharmacovigilance and key terms

The pharmacovigilance process was developed by national drug regulatory agencies, including the US Food and Drug Administration (FDA), to ensure safe and effective medicines for the general public.¹ Pharmacovigilance (Figure 1) principally involves the identification and evaluation of safety signals associated with the use of a medicinal product, and refers to ‘all scientific and data gathering activities relating to the detection, assessment, and understanding of adverse events’.² The process of risk assessment during a medicine’s clinical development, including the identification of AEs as adverse reaction rates for drug exceed the placebo rate, has been reviewed in detail and is well understood.^{3–5} The process of assessing

medicinal product risk in the postmarketing setting is complicated by the lack of a placebo comparator and use by patients with comorbid conditions and those being treated with concomitant medicinal products. Safety signals, defined by the FDA as AEs that exceed what would be expected to be associated with a product’s use based on what has been reported in clinical trials,² may arise in the postmarketing setting from passive and active surveillance, or from additional preclinical and clinical data, including those from other products in the same therapeutic class. Identification of a safety signal necessitates additional investigation to determine treatment causality and whether the safety signal represents a potential safety risk that requires action and communication to the patient and HCPs.

Multiple national and international regulatory agencies and their centers for the study of AEs,¹ including the FDA, World Health Organization (WHO), and the European Medicines Agency (EMA), have agreed to cooperate and share information on drug safety issues,⁶ and each provides separate, but overlapping, definitions for key terms involved in the pharmacovigilance process (Table 1).^{1,7–10} Despite the general consistency of concepts across agencies, communication between HCPs, regulatory parties, and industry professionals is complicated by the diversity of terms, which are often used interchangeably in clinical practice and among different healthcare systems.¹¹ For example, ‘safety’ and ‘tolerability’ are sometimes used synonymously. Safety typically refers to AEs that are serious or classified as ‘severe’ by the HCP, whereas tolerability usually refers to unpleasant but less consequential AEs.⁵ Furthermore, HCPs commonly use the term ‘side effect’ much more frequently than other terms, such as adverse drug reactions (ADRs), whereas the regulatory term is AE. Regardless of the term used, AE, ADR, or side effect, all refer to undesirable effects associated with medication use and should prompt participation in the pharmacovigilance process. In this article, we will use the term AE.

Collection of safety information during drug development

Collection of safety information begins during preclinical studies, where potential safety concerns may be identified based on the pharmacokinetic and pharmacodynamic profile of the drug,

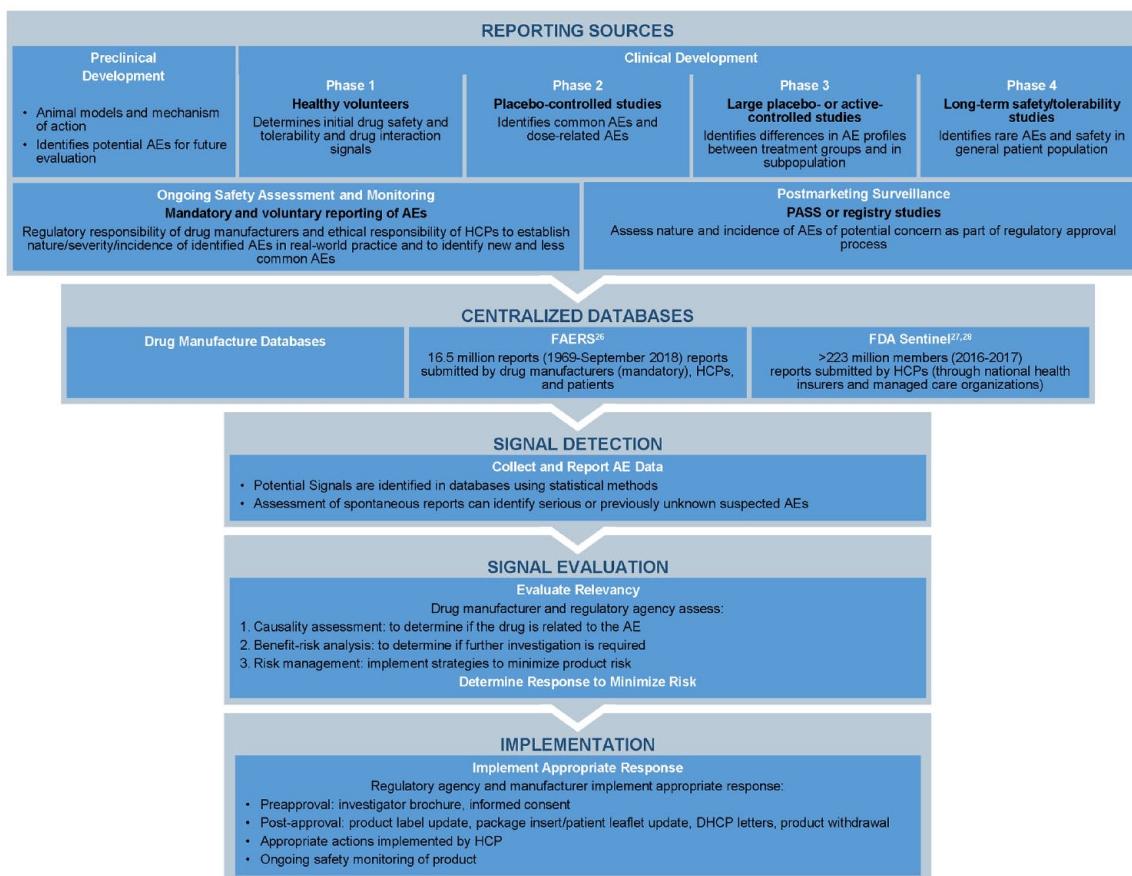


Figure 1. An overview of the pharmacovigilance process.

AE, adverse event; DHCP, Dear Health Care Provider; FAERS, FDA Adverse Event Reporting System; FDA, US Food and Drug Administration; HCPs, health care providers; PASS, post-approval surveillance study.

the biology of the drug target,¹² and possible drug-receptor interactions.¹³ The preclinical data collected during this phase provide information that can be used in clinical trials to help determine the bioavailability and maximum tolerated dose of the drug, which can inform dosing for subsequent clinical trials.¹⁴ Clinical studies performed in select targeted patient populations, provide information on dose-related effects, drug interactions, and provide comparisons with placebo, giving information on the types, frequency, severity, and potential drug-relatedness of observed AEs.^{5,15}

Clinical trials are subject to regulatory safety reporting requirements by the FDA.¹⁵ Investigators are required to report to study sponsors and institutional review boards any AEs, defined by the FDA as ‘unfavorable changes in health, including abnormal laboratory findings, that occur in trial participants during the clinical

trial or within a specified period following the trial’¹⁶ thought to be caused by the drug and any serious or unanticipated AEs regardless of their assessment of causality, to enable reporting by the study sponsor to regulatory agencies.³ During clinical trials, a summary of all preclinical and clinical data to date, including safety findings, is provided to investigators in the Investigator’s Brochure with the goal of facilitating understanding of all information related to the product.¹⁷ In addition, study protocols must have a detailed description of safety procedures on which site staff are required to be trained to meet their obligations for recording safety information.¹⁸

In the clinical setting, safety reporting begins when there is identifiable patient exposure to the product, an identifiable reporter, and an AE.¹⁸ If possible, the causality of the reported event should be established. The severity (ie, the intensity of the AE symptoms, mild to severe),

Table 1. Summary of safety-related terms.

Term	WHO definition ^{1,7}	FDA definition ⁸⁻¹⁰	Example
Side effect	'Any unintended effect of a pharmaceutical product occurring at doses normally used by a patient which is related to the pharmacological properties of the drug'	'Unwanted or unexpected events or reactions to a drug'	Induction of weight gain by a drug
ADR	'A response to a medicine which is noxious and unintended, and which occurs at doses normally used in man'	'Any adverse event cause by a drug'	Birth defects associated with administration of a drug during pregnancy
Unexpected ADR	'An adverse reaction, the nature or severity of which is not consistent with domestic labelling or market authorization, or expected from characteristics of the drug'	'An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or it is not listed at the specificity or severity that has been observed [...]'	
AE	'Any untoward medical occurrence that may present during treatment with a medicine but which does not necessarily have a causal relationship with this treatment'	'Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related'	Hypertension developed during a clinical trial
Serious AE or ADR	'Any event that is fatal; life-threatening; permanently/significantly disabling; requires or prolongs hospitalization; causes a congenital anomaly; requires intervention to prevent permanent impairment or damage'	'An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: Death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect'	Serious or potentially fatal hypersensitivity reactions, which may lead to a Boxed Warning addition to the prescribing label.
Signal	'Reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously'	'Reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented; a newly identified at-risk population; new unlabelled adverse events; an observed increase in a labelled event or a greater severity or specificity; new interactions, usually supported by multiple case reports'	Possible increased risk of nephrolithiasis with drug use

ADR, adverse drug reaction; AE, adverse event; FDA, US Food and Drug Administration; WHO, World Health Organization.

seriousness or medical significance (ie, AE posing a threat to patient's life or function or resulting in hospitalization or prolonged hospitalization), and expectedness of the AE should also be considered.¹⁸ Any AE and any suspected unexpected serious adverse reaction (SUSAR) must be reported to the sponsor; the sponsor is then responsible for determining if the SUSAR is reasonably unexpected, and the reporting of those

that are both serious and unexpected directly to the FDA.⁸ All AE reports are submitted electronically to the FDA Adverse Event Reporting System (FAERS) database within a specified time period (eg, SUSAR associated with the use of a drug under an Investigational New Drug application must be reported within 15 calendar days after receiving the information and within 7 calendar days after initial receipt of information for fatal or

life-threatening AEs).^{8,19} Data and safety monitoring boards provide additional safety process oversight independent of the study sponsor and investigators and consist of subject matter experts with no vested interest in the clinical trial or specific treatment, who upon regular review of unmasked data in an ongoing clinical trial recommend whether the trial should be continued, altered, or terminated.^{15,20}

Collection of safety information in the postmarketing environment

At the time of market approval, the risks and adverse effects associated with a medicinal product are not entirely known. Therefore, postmarketing safety surveillance is critical for ensuring safe and appropriate use of medicinal products. Safety data from clinical trials and postmarketing reports differ

in the denominator data (Table 2), or the availability of the number of people using the drug.²¹ In controlled clinical trials, the clearly defined patient population allows for the calculation of AE incidence rates and for HCPs to understand the likelihood of an event. Given the limited size of the study population, clinical trials are often inadequately powered to detect either multiple or rare AEs. Furthermore, the settings and patient characteristics associated with the real-world use of a drug differ from the conditions under which drugs are tested and approved for market use. Thus, postmarketing AE reporting is often used to provide increased identification, evaluation, and reporting of rare events.^{6,22} New events may be identified in high-risk individuals normally excluded from clinical trials, and the seriousness of some AEs may be re-evaluated with additional information from a larger population.^{6,23}

Table 2. Overview of the differences in safety data collected in a clinical trial and during postmarketing surveillance.

	Clinical trial data ^{5,15}	EHR/claims database ²⁴⁻²⁶	FAERS database ^{6,21,27}	FDA sentinel ²⁸
Data collection				
Denominator known	Yes	Yes	No	Yes
Systematic reporting	Yes (trained investigators and clinical oversight)	Limited (capturing data in EHR/claims database)	No (voluntary reporting)	Limited (capturing data in EHR/claims database)
Diverse population	No	Yes	Yes	Yes
Data analysis				
Comparisons	Yes (limited to study comparisons)	Possible (across all drugs; limited by consistency of data capture)	Not recommended (incomplete reporting and unknown denominator)	Possible (across all drugs; limited by consistency of data capture)
Data mining	No	Yes	Yes	Yes
Limitations	Population size and length of follow-up	Consistency of data capture	Lack of systematic reporting; AEs may not be reported	Data come from claims, may poorly relate to patient outcomes; data integrity and reliability
Strengths	Systematic data capture by trained investigators	Size of database; identifies uncommon AEs in real-world use	May identify uncommon AEs, if reported; size of database allows safety signal identification	Size of data network; allows for highly sophisticated statistical methods

AE, adverse event; EHR, electronic health record; FAERS, FDA Adverse Event Reporting System; FDA, US Food and Drug Administration; HCP, healthcare professional.

In the United States, drug manufacturers are required by the FDA to conduct ongoing safety evaluations and periodically review and analyze their safety databases. These requirements and regulations provide a mechanism for the FDA to detect early warning signs of potential threats to public health. Postmarketing safety reports must be expedited for AEs that are both serious and unexpected, regardless of source. For non-serious (regardless of expectedness) AEs and serious expected AEs, non-expedited reports are filed quarterly for the first 3 years after approval and then annually.²⁹ Furthermore, manufacturers are required to examine reports from the scientific literature and marketing experience in other countries.⁸ Drug manufacturers are required to collect, analyze, and report AEs to all countries where the product is marketed, working closely with the regulatory agencies in those countries to identify and understand the safety signals.

AEs can be reported directly to the manufacturer by patients or HCPs *via* direct submission to registries. While reporting to national registries and the FDA is voluntary for HCPs, drug manufacturer reporting is required by law in most jurisdictions, including the United States (Figure 1).^{18,29} Thus, most drug manufacturing companies establish robust programs for the public collection of AEs, which are publicized on patient websites, in HCP offices, and *via* social medial platforms.

Safety reports are derived from postmarketing pharmacovigilance, which comprises both passive and active surveillance, inform HCPs for the early detection of drug safety problems and improve the selection and rational use of drugs.² Passive surveillance relies on voluntary reporting of safety information by HCPs and patients/caregivers to drug manufacturers or directly to the FDA to further characterize the safety profile of drugs in the real-world setting.^{6,18} In addition to the safety databases maintained directly by drug manufacturers,^{2,30} computerized databases for collecting spontaneous postmarketing safety reports are managed by the regulatory agencies, including FAERS²⁷ and the FDA Sentinel System^{31,32} in the United States, with comparable systems managed by WHO (VigiBase) and EMA (EudraVigilance).^{33,34} These centralized databases also enable voluntary reporting by HCPs and consumers, either directly (eg, in FAERS) or *via* electronic health records (EHRs) provided by healthcare organizations (FDA

Sentinel).^{29,32} Case reports submitted to centralized databases are also assessed to identify possible safety signals for marketed drugs.^{27,33}

Safety data collected from postmarketing surveillance lack the structure of data collected from controlled clinical trials,³⁵ which has active follow-up involving specific protocols and reporting requirements, and where there is typically a comparator group not receiving drug. Not all patients report AEs to their physician²¹ and the multiplicity of drug and disease state factors in the real-world setting may make it difficult to attribute causality and create uncertainty in reporting.²⁴ Furthermore, the time required to complete AE reporting forms provided by the FDA (estimated 40 min) may limit voluntary reporting.³⁶ As a result, only an estimated 1–10% of significant AEs are reported by physicians.³⁷ Despite these limitations, routine pharmacovigilance spontaneous reporting can be sufficient for postmarketing risk assessment for most products.²

In instances where serious safety risks have been identified pre- or post-approval or when at-risk populations have not been adequately studied, the FDA may recommend pharmacovigilance plans. In contrast to the largely voluntary basis of passive pharmacovigilance, which relies on spontaneous safety reporting that contains limited information on patient characteristics, active pharmacovigilance monitors AEs through an ongoing preorganized process of systematic collection of clinical information on a population of patients who receive drugs post-approval. Active pharmacovigilance can be used to provide a more complete reporting of health events with detailed information about patient populations, including polypharmacy, comorbidity, and sociodemographic characteristics. Thus, after drug approval, the sponsor may conduct long-term safety, tolerability, and outcome studies (phase 4 studies) to better assess rare AEs and drug interactions.⁵ Although these phase 4 studies may entail post-approval efficacy studies, active pharmacovigilance usually entails dedicated PASS.

PASS, which can be voluntary or a mandatory requirement following approval of a drug, commonly for novel drugs that have been through an accelerated approval pathway,³⁸ may take the form of observational studies, randomized post-marketing surveillance safety trials, or registries.^{18,27} PASS used as part of safety surveillance

allows for consistent determination of exposure, in populations with large and known patient denominators, and relatively complete event recording by HCPs.²⁵ PASS typically enrolls a more diverse population than randomized controlled trials, including patients who are elderly, have comorbidities, or who use concomitant medications – those who may have been excluded in clinical trials.³⁹ Despite the usefulness of patient registries ('organized systems using observational methods to collect uniform data on a population defined by a particular disease, condition, or exposure, and that is followed over time')⁴⁰ to collect either solicited (part of the uniform collection of information in the registry) or unsolicited (volunteered information or otherwise not required in the case report form) AEs,¹⁸ they are not a mandatory requirement and remain underused when available.^{40,41} When patient registries are available, any AEs received by the drug manufacturer *via* this mechanism must be reported to the FDA as previously described. There is a growing movement promoting the integration of EHR with existing registries, which would provide a more robust data set including prescriptions and pharmacy data.⁴² Data mining of claims databases containing a summary of healthcare services provided, patient demographics, diagnoses (including diagnoses related to potential AEs), procedures, outpatient visits, hospitalizations, and prescriptions⁴³ can help identify drug-event pairs,²⁶ and coupled with pharmacovigilance, may lead to improved detection of clinically important AEs.^{26,44,45} Nevertheless, analyses of claims data can only point toward a correlation of events and cannot attribute causality, especially because claims data are generally not clinically validated.

There are also potential sources of safety data outside of the healthcare system. Social media is increasingly becoming a source that can be used to identify patterns in medication use and AEs. Patients often post their direct experiences to social media channels, as well as health-related websites. These sources provide individual experiences with additional data, including environmental factors, prescription deviations, and licit and illicit polypharmacy that can be missed by standard pharmacovigilance surveillance processes. Despite the large volume of easily accessible data provided by social media, the identification of safety signals can be limited by challenges inherent in the system. Data are

unstructured and without standardized terminology, resulting in misspellings, abbreviations, or slang language used to discuss drugs and medical conditions. The anonymity of the forums also prevents verification of the validity of such reports. However, the volume of data can help identify potential areas of concern that would merit follow-up investigation using more rigorous methodology and databases.

Safety reporting and changes to drug labels

All scientific information collected throughout the drug development process is used to draft prescribing information (also known as the package insert or drug label).⁴⁶ During the initial approval process, the FDA requires submission of a draft label that includes a number of safety-related sections, namely Contraindications, Boxed Warnings, Warnings, Precautions, and Adverse Reactions,⁴⁷ with specific guidance for each of these sections (Table 3).^{48–50} According to the Physician Labeling Rule of 2006, these sections must contain all relevant necessary information for the safe and effective use of the product.⁴⁶ Drug manufacturers are required to review the label at least annually for any outdated information, and update the label when new information becomes available that may cause it to become inaccurate, false, or misleading.⁴⁶ New safety information, defined as 'information derived from a clinical trial, an adverse event report, a post-approval study, or other scientific data deemed appropriate by the FDA', about serious safety risks identified or assessed after drug approval or last assessment,⁵¹ is assessed by a multidisciplinary team formed by the FDA. The expectation is that the appropriate section of the label (eg, Boxed Warnings, Contraindications, Warnings and Precautions, Drug Interactions, Adverse Reactions) will be revised accordingly based on the outcome of those assessments.⁵¹

Potential safety signals identified in clinical trials and during postmarketing pharmacovigilance are assessed by qualitative and quantitative analyses, followed by a clinical assessment with regard to its impact on the overall safety profile of the drug.² Initially, individual reports are qualitatively examined by the clinician to make a judgment call regarding causality based on their clinical expertise on a case-by-case basis in an unstructured analysis. Qualitative analyses can be used to determine degree of relatedness based on

Table 3. Overview of drug label sections.

Label section	FDA guidance ^{48,50}	Notes
Boxed Warning	'A boxed warning is ordinarily used to highlight for prescribers one of the following situations: <ul style="list-style-type: none">• There is an adverse reaction so serious in proportion to the potential benefit from the drug (eg, a fatal, life-threatening or permanently disabling adverse reaction) that it is essential that it be considered in assessing the risks and benefits of using the drug OR <ul style="list-style-type: none">• There is a serious adverse reaction that can be prevented or reduced in frequency or severity by appropriate use of the drug (eg, patient selection, careful monitoring, avoiding certain concomitant therapy, addition of another drug or managing patients in a specific manner, avoiding use in a specific clinical situation) OR <p>FDA approved the drug with restrictions to ensure safe use because FDA concluded that the drug can be safely used only if distribution or use is restricted [. . .]'</p>	If a Boxed Warning is relevant for an entire drug class, then the FDA may require that it is placed in all approved drugs belonging to that class (eg, benzodiazepines and 'risk of misuse, addiction, physical dependence, and withdrawal reactions' ⁴⁹)
Warnings and Precautions	'[Intended to] identify and describe a discrete set of adverse reactions and other potential safety hazards that are serious or are <i>otherwise clinically significant</i> because they have implications for prescribing decisions or for patient management'	For each ADR, there should be a succinct description of the reaction and outcome, and a numerical estimate of its risk, any known risk factors and mitigation steps
Contraindications	'A drug should be contraindicated only in those clinical situations for which the risk from use clearly outweighs any possible therapeutic benefit'	Includes observed and anticipated ADRs, which should be briefly described along with consequences
Adverse Reactions	'[Required to] list the adverse reactions that occur with the drug and with drugs in the same pharmacologically active and chemically related class, if applicable'	Separate subsections for adverse reactions identified in the clinical trial and postmarketing setting The frequency of AEs reported in tabular form on the product label will depend on a number of factors; the cutoff frequency should be indicated Limited to events for which there is some basis of a causal relationship

ADR, adverse drug reaction; AE, adverse event; FDA, US Food and Drug Administration.

standardized criteria such as the timing of the reaction relative to drug exposure, dose response, dechallenge/rechallenge, drug pharmacology, or established AEs caused by related drugs.⁵² Similarly, lists of spontaneously reported AEs can be scanned and investigated in a more systematic manner using the same qualitative-based assessments. Automated statistical methods can be used to interrogate large databases to make signal detection more efficient,^{2,45,53} but can be limited by confounders and biases inherent in the data and the increased risk of false positives. Thus, a

combination of quantitative and qualitative criteria may be needed to determine the safety data to be included in the drug label. Guidance on safety signal identification, pharmacoepidemiologic assessment and safety signal interpretation, and pharmacovigilance plan development is provided in the Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment.² Based on safety signals in the clinical development trials or 'new safety information', the FDA may require PASS, registries, or risk evaluation and mitigation strategies.^{11,54}

Potential safety signals are evaluated by the drug manufacturer using preclinical, clinical, postmarketing, and epidemiology data (Figure 1).² For each safety signal, an assessment of background rates of events may be undertaken in the general population or in a subpopulation with characteristics similar to those of the population using the drug. A causality assessment is undertaken to determine if the AE is likely to be related to the drug, and a risk–benefit analysis is undertaken to determine if further investigation is required.^{2,53} If necessary, mandatory risk evaluation and mitigation strategies are implemented to minimize the risk of use.^{30,53,55}

Regulatory bodies were established to protect consumers from harm, and as such, timely communication to stakeholders and/or modification of safety information in product labels may be considered necessary based on postmarketing surveillance data. Regardless of the result of the manufacturer's assessments, it is mandatory to report all AEs to FAERS and when a safety signal indicates a potential safety risk, the manufacturer is required to submit all available safety information and analyses performed from preclinical findings to current observations to the FDA.² The FDA will then make its own assessment of the safety signal and any potential safety risk, taking into account the information provided by the sponsor and any additional relevant information known to the FDA. FAERS data are assessed by clinical reviewers in the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research, often as aggregated data mined to identify safety signals that require further investigation.^{2,29,56} Further assessment is based on factors such as reporting frequency, comparison to placebo or background rate, extent of dose response, consistency with pharmacology of the drug, relative timing of reaction and drug exposure, and the safety profile of related drugs. The FDA uses these data internally to issue safety warnings, update drug information labels, and restrict the use of or remove medications from the market.

If the FDA reviewers determine enough evidence has been presented or that a very serious AE has occurred, resulting action can include a product label change. When weighing the evidence for a causal relationship to determine if new safety information should be included in labeling, the threshold for inclusion is lowered the more

relevant the information is; the higher the medical seriousness of the risk; the greater the clinical utility of new information; the availability of alternative treatments; the extent of use; and based on the use of the product (ie, used for relatively trivial conditions, for treatment of symptoms, or for prevention vs for life-threatening conditions).

Although label changes are the primary means of communicating new safety information, drug safety communications can also include early notices about safety issues that are under review (public health advisories), Dear Health Care Provider (DHCP) letters, or public announcement from the FDA through the media for new safety information that represents timely or significant health concerns. Examples of when the FDA may recommend the issuance of a DHCP include the following: previously unknown serious or life-threatening AEs, new information about a known AE that is clinically important, identification of a subpopulation at greater risk for AEs from the drug or in which the drug is contraindicated, a drug–drug interaction or medication error that can result in a serious or life-threatening AE, or a new or modified risk evaluation and mitigation strategy implementation.⁵⁷ If the drug is deemed to be unsafe by the FDA under the conditions of use approved during initial application, approval can be withdrawn, removing the product from the market.⁵⁸ In addition to DHCP letters, national drug regulatory bodies can issue medicine alerts, media statements, and patient information leaflets, often in collaboration with the drug manufacturer.¹

Since January 2016, the CDER has managed the Drug Safety–related Labeling Changes database.⁵⁹ Labeling updates are common, with more than 50% of label changes arising from spontaneous reports.⁶⁰ There is an average of 400–500 product label changes per year based on approximately 500,000 AE reports received by the FDA each year.⁵⁶ Each change should not be viewed as a significant event, as label changes and recurring revisions are standard practice under the current post-approval pharmacovigilance system.

The FDA must decide how broadly an advisory, warning, or label change should be applied when risk information is only available for select products within a therapeutic class. The decision to issue a drug- or class-level label change often depends on the magnitude of potential harm

associated with the AE and the level of evidence available on drug differences, including pharmacokinetics or other contextual factors. Class-wide label changes are usually applied the more serious the AE or based on clear and overwhelming evidence that the AE is the result of the function of the pharmacologic activity of the drug rather than specific feature of the individual medication. Lacking compelling evidence to justify a class-wide regulatory action, less-severe changes can be applied to a single medicinal product within a therapeutic class. Since regulatory actions are necessarily dependent on the available evidence, there is the potential for labeling changes to be biased toward first-in-class drugs which, with more time on the market, have more data available in which safety signals can be identified. It has been estimated that the time lag for Black Box Warnings among drugs of the same class range from 2 to 170 months, with a median of 66 months.⁶¹ Such differences in the issuance or timing of label changes may be justified or may simply reflect differences in the available accumulated evidence for different agents. However, absences or asynchronous label changes among same-class medicinal products can create confusion for prescribers and can differentially favor drugs unnecessarily. Interpretation of label revisions should be done in context and with an understanding of the limitations present in current pharmacovigilance systems.

Limitations to the pharmacovigilance system

Notwithstanding the systematic capture of data in clinical trials, AE reporting in the literature is inconsistent,⁶² and frequently incomplete or inadequate.⁵ Safety signals may not be properly identified for various reasons, including small treatment populations, short treatment durations, patient population homogeneity, and insufficient statistical power to detect differences between treatment arms. Furthermore, AEs may be coded inaccurately, with differences between AEs and ADRs further complicating characterization.^{21,63}

To date, most label changes have been the result of findings from passive postmarketing surveillance, which is limited by the voluntary nature of AE reporting. While most FAERS reporting was submitted by drug manufacturers, less than 10% was submitted directly by HCPs or consumers.²³ Voluntary AE reporting has limitations that differ

for those associated with active surveillance performed by the drug manufacturer throughout the drug lifecycle. For example, postmarketing reporting by HCPs may lack sufficient information to adjudicate AE causality or relationship to drug, creating uncertainty over whether the reported event could be considered drug related.^{21,27} In unsolicited AE reporting, causality is assumed, not assessed,^{64,65} and follow-up reports are not required unless new information arises,⁶⁵ making it challenging to determine causality if the information provided is incomplete or confounded.² When AEs are reported, the lack of standardized definitions used for postmarketing reporting by HCPs³⁶ and unverified information in these reports²⁷ may contribute to inaccuracies within the reports.^{6,21,27} Given the redundant AE reporting channels, multiple reports may be submitted for a single AE event (ie, by the consumer, the HCP, and the drug manufacturer),²⁷ owing to several drug manufacturer-initiated contact points with patients or HCPs that trigger AE reporting, such as prescription refill reminders, insurance coverage assistance, nurse hotlines, and patient education programs.

Involuntary bias in the events commonly reported by HCPs and patients may impact the rates at which some AEs are reported. Common, expected AEs associated with a drug may go unreported.⁶ AEs with a long latency period may not be identified as drug-related, and thus not reported.⁶ Some reported AEs may be coincidental, reflect symptoms of the disease being treated, or be attributed to misuse of the drug, rather than an AE per se.²⁴ AE reporting rates in clinical practice can also be influenced by external factors such as time on market²⁷ or popular news coverage. First-in-class agents tend to be subjected to close postmarketing surveillance by regulatory agencies and HCPs.^{66,67} Negative publicity about any given event may affect patient and HCPs perception of ‘safety’ and therefore influence reporting.^{27,24} Importantly, manufacturers and HCPs often have different definitions for events and therefore may not report them as AEs to either FAERS or to the drug manufacturer.

Some of the inaccuracies associated with passive postmarketing reporting may be inherent with the national databases themselves. Some, such as FAERS, do not have a known denominator, limiting the ability to quantify AE risk and incidence rate.^{6,21} Contributing parties are not the

same across databases; for example, drug manufacturers contribute to FAERS, whereas FDA Sentinel receives EHR from healthcare organizations.^{29,32} The means of AE surveillance (ie, active vs passive) and reporting (ie, solicited vs unsolicited) frequently differ between databases.⁶⁸ As there is no cross-referencing between registries, the same AE can be entered into multiple databases from overlapping sources. A notable example is when a safety signal detected in FAERS, which is a single database, prompts a search in FDA Sentinel, a distributed data network of participating organizations,²⁸ therefore giving duplicate results.

Claims databases or EHR databases, which are primarily designed to inform clinical decisions and/or support administrative functions, have their own inherent limitations, including possible biases and confounding issues.⁶⁹ Data stem from clinical encounters and therefore any events of interest that do not result in the use of healthcare services are not captured. Prescription database fills and refills captured in these databases do not directly reflect actual medication use resulting in uncertainty about medication exposure. Claims databases, in particular, may be biased toward the insured population.^{24,70} Other issues such as coding errors and differences across healthcare systems may impact how data are captured prior to analysis.

Conclusion

Pharmacovigilance is an essential ongoing responsibility of all drug manufacturers, HCPs, and consumers of drug therapy to ensure the continued safety of available medicines.¹ The approaches highlighted in this review are used to ensure relevant safety signals are captured throughout a drug's lifecycle, from clinical development to use in clinical practice.⁷¹ For a more complete understanding of the potential safety concerns associated with a drug, the full repertoire of pharmacovigilance tools should be used; clinical trials identify the most common AEs, but safety signals detected by postmarketing surveillance, further evaluated by reviewing published literature or through clinical evaluation, can be helpful in identifying infrequent AEs.⁷¹

While AEs are captured in a systematic manner across standardized populations in controlled clinical trials,⁵ identification of AEs in clinical

practice can be more challenging. Gathering of real-world safety data largely relies on the voluntary reporting by HCPs to the drug manufacturers or directly to the FAERS database, and active reporting to the FDA Sentinel database based on EHR data from healthcare organizations. Nevertheless, the lack of a clear denominator in postmarketing surveillance limits the comparison of AEs across drugs and drug classes, as reporting rates cannot be considered to reflect incidence rates,² and makes causality assessment difficult owing to incomplete information and lack of follow-up.^{2,65} Postmarketing surveillance databases have been established to collect important safety information. In parallel, assessment of EHR and claims databases are used to help verify clinical signals detected from spontaneous reports recorded in the postmarketing surveillance databases.⁷²

Together, the toolkit of pharmacovigilance (clinical trial reporting, postmarketing surveillance, survey of claims databases, EHR, and PASS) provide a comprehensive approach for early identification of safety signals, ensuring the safe and effective use of drugs. To have optimal benefit, all participants in the healthcare system, including HCPs and consumers, must meaningfully engage in the process of pharmacovigilance and integrate it into their everyday practice.^{11,73} The promotion of improved reporting of AEs in clinical practice will help ensure a better understanding of AEs by healthcare professionals.^{74,75}

Declarations

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Not applicable

Consent for publication

Not applicable

Author contributions

Sylvia Lucas: Conceptualization; Writing – review & editing.

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AA is an employee and stockholder of Novartis.

FX and **MSN** were employees and stockholders of Amgen Inc. at the time of the study.

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Competing interests

SL has served as a consultant or advisor for Allegan/AbbVie, Amgen, Biohaven, Impel, Eli Lilly, Lundbeck, Teva; and is on the Pharmacy & Therapeutics Committee for Premera Blue Cross/Blue Shield.

JA has served as a consultant (honoraria for independent consulting) for Amgen, AbbVie, Biohaven, Eli Lilly and Company, Lundbeck, Teva, Impel, Satsuma, Theranica, Axsome, Neso, GlaxoSmithKline, Aeon, and Medscape; has stock ownership with CtrM; served on the speakers bureau (honoraria for promotional speaking) for Allergan/AbbVie, Amgen, Biohaven, Eli Lilly and Company, Lundbeck, Teva; provided editorial services (honoraria) for Current Pain and Headache Reports (section editor), Unusual Headache Syndromes, NeurologyLive, and SELF (medical reviewer); and received clinical trial grants: (fees to institution) from American Migraine Foundation, Allergan, Biohaven, Eli Lilly and Company, Satsuma, and Zosano.

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