

CHAPTER 7

FUNDAMENTALS OF PHARMACOVIGILANCE

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Abstract

Pharmacovigilance is the foundational science of drug safety, built upon a precise lexicon that distinguishes between coincidental medical occurrences and true drug-induced harm. The discipline begins with the critical distinction between an Adverse Event (AE), which is simply a temporal association between a drug and a negative outcome, and an Adverse Drug Reaction (ADR), which implies a suspected causal link. The regulatory machinery of reporting is triggered by specific filters, the most important being the Seriousness Criteria. Six specific outcomes death, life-threatening conditions, inpatient hospitalization, persistent disability, congenital anomaly, and medically significant events elevate an event to the status of a Serious Adverse Event (SAE), mandating expedited reporting to health authorities. The intellectual process of Causality Assessment is essential for determining the likelihood of drug attribution, utilizing structured tools like the Naranjo Probability Scale and the WHO-UMC system to evaluate dechallenge and rechallenge data. Finally, the concept of Expectedness acts as the regulatory gatekeeper. The Reference Safety Information, such as the Investigator's Brochure in trials or the Summary of Product Characteristics in post-marketing, serves as the legal baseline for determining whether a serious reaction is "unexpected" and thus qualifies as a Suspected Unexpected Serious Adverse Reaction (SUSAR) requiring immediate, expedited notification to global health authorities.

Keywords: *Adverse Drug Reaction (ADR), Seriousness Criteria, Causality Assessment, Expectedness, SUSAR*

Learning Objectives

After completion of the chapter, the learners should be able to:

- Distinguish between an Adverse Event (AE) based on temporal association and an Adverse Drug Reaction (ADR) based on causal relationship.
- Identify the six regulatory criteria that classify an adverse event as "Serious" (SAE) for expedited reporting purposes.
- Apply causality assessment tools, such as the Naranjo Probability Scale and the WHO-UMC system, to determine the likelihood of drug attribution.
- Assess the "Expectedness" of an adverse reaction by comparing it against the approved Reference Safety Information (IB or SmPC).
- Explain the implications of Suspected Unexpected Serious Adverse Reactions (SUSARs) on regulatory reporting timelines.

DEFINITION AND SCOPE

Pharmacovigilance is often described as the science of drug safety, but at its core, it is the rigorous science of causality. Before a safety physician or a regulatory authority can determine if a pharmaceutical product is dangerous, they must first distinguish between negative health outcomes that happen to a patient and negative health outcomes that happen because of a drug. This critical distinction forms the boundary between an Adverse Event (AE) and an Adverse Drug Reaction (ADR). While these terms are frequently used interchangeably in casual clinical conversation, in the regulatory context of the FDA, EMA, and the International Council for Harmonisation (ICH), they have precise, distinct legal definitions that dictate how safety data is collected, analyzed, and reported.

Temporal Association of The Adverse Event (AE)

An Adverse Event is the broadest and most inclusive term used in the field of drug safety. The International Council for Harmonisation (ICH) guideline E2A defines an Adverse Event as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal

relationship with this treatment.

The operative phrase in this definition is that the event does not necessarily have to have a causal relationship. An Adverse Event is defined strictly by chronology, not by etiology. It is a temporal association. If a patient swallows a study tablet at nine in the morning and subsequently breaks their leg falling down a flight of stairs at ten in the morning, that broken leg is recorded as an Adverse Event. It occurred after the drug was administered. At the initial stage of data collection, it is irrelevant whether the drug caused the fall by inducing dizziness or hypotension, or if the patient simply tripped on a loose carpet. The mere fact that the medical event happened during the treatment period qualifies it as an Adverse Event. This definition covers any unfavorable and unintended sign, including an abnormal laboratory finding, a symptom, or a fully developed disease.

This broad scope is intentional and strategic. In the early stages of drug development, researchers do not yet know the full safety profile of the molecule. If investigators were allowed to filter out events they subjectively believed were unrelated, they might inadvertently discard subtle safety signals. For instance, if ten patients in a large trial break their legs, an investigator looking at a single patient might dismiss it as a random accident. However, the aggregate data might later reveal that the drug causes severe osteoporosis or loss of balance. The system casts a wide net to ensure no potential safety signal is ignored by capturing everything as an AE first,, regardless of how implausible the connection might initially seem.

The Adverse Drug Reaction (ADR): A Causal Link

An Adverse Drug Reaction represents a specific subset of Adverse Events where the relationship to the drug is more than just temporal. It is defined as all noxious and unintended responses to a medicinal product related to any dose. The defining characteristic of an ADR is the existence of a causal relationship between the drug and the event. In other words, an ADR is an Adverse Event where the drug is suspected to be the driver of the pathology.

Table 7.1: Distinguishing Adverse Events from Adverse Drug Reactions

Feature	Adverse Event (AE)	Adverse Drug Reaction (ADR)	Illustrative Example
Definition	Any untoward medical occurrence in a patient administered a drug; does not necessarily have a causal relationship.	A noxious and unintended response to a drug where a causal relationship is at least a reasonable possibility.	AE: Patient breaks leg skiing while on Statin. ADR: Patient develops muscle pain (myopathy) while on Statin.
Basis of Association	Temporal: The event happened <i>after</i> the drug was taken.	Causal: The drug is suspected to be the <i>cause</i> of the event.	Nausea occurring 30 minutes after taking a pill vs. Nausea occurring after eating spoiled food.
Reporter's Role	Records all events regardless of opinion (in clinical trials).	Makes a judgment call on attribution ("Related" vs "Not Related").	Investigator records "Headache" but marks causality as "Unrelated/Due to stress."
Regulatory Action	Included in annual safety summaries and databases.	Evaluated for expedited reporting (SUSAR) and label updates.	High frequency of ADRs leads to "Warning" section updates.

The transition from classifying something as an AE to an ADR involves a medical judgment call based on the concept of reasonable possibility. If the investigator or the sponsor

believes there is a reasonable possibility that the drug caused the event, it is escalated to the status of an ADR. To illustrate this distinction, one might consider a patient taking a new antihypertensive medication who develops severe nausea. If it is discovered that the patient ate expired seafood for lunch just before the nausea started, the investigator would likely determine the cause to be food poisoning, unrelated to the drug. In this narrative, the nausea remains an Adverse Event but is not classified as an Adverse Drug Reaction. Conversely, if the patient has no other dietary changes and the nausea recurs every time they take the pill a phenomenon known as a positive rechallenge the investigator would suspect the drug is irritating the stomach lining. In this narrative, the nausea is classified as an Adverse Drug Reaction.

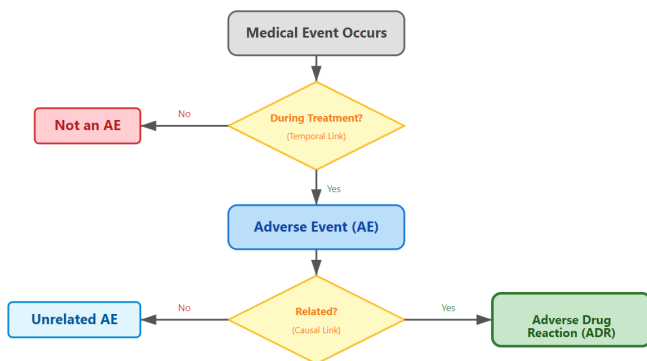


Figure 7.1: AE vs. ADR Decision Tree

Pre-approval versus Post-approval Definitions

The nuances of defining an ADR shift slightly depending on the stage of the drug's lifecycle. During clinical trials, or the pre-approval phase, the safety profile is not fully established, so the threshold for calling something an ADR is conservatively low. The ICH E2A guideline states that if the relationship cannot be ruled out, it should be treated as an ADR. The focus here is on the suspected nature of the reaction, ensuring that uncertainty is resolved in favor of safety reporting.

Once a drug is approved and available on the market, the definition broadens significantly under the ICH E2D guideline. In the post-marketing setting, an ADR encompasses any response to a drug which is noxious and unintended. Crucially, this definition includes not only reactions arising from the use of the drug within the terms of the marketing authorization but also reactions arising from use outside the terms of the marketing authorization. This means that adverse outcomes resulting from overdose, misuse, abuse, and medication errors are considered ADRs in the post-marketing world. For example, if a patient accidentally overdoses on a painkiller and suffers liver failure, this is considered an ADR because it is a noxious response to the molecule, even though the usage was incorrect. This shift reflects the reality that in the real world, drugs are not always used exactly as prescribed, and the safety monitoring system must account for these risks.

The Importance of the Distinction

Distinguishing between AEs and ADRs is not merely a semantic or academic exercise; it drives the entire regulatory reporting engine and shapes the medical information provided to the public. The primary consequence of this distinction lies in reporting obligations. Sponsors are generally required to report all Adverse Events in the final Clinical Study Report to show the overall health of the study population. However, they are legally mandated to significantly expedite the reporting of serious Adverse Drug Reactions to health authorities. A serious Adverse Event that is determined to be unrelated to the drug, such as a passenger injured in a car accident, does not require expedited reporting to the FDA. However, a serious Adverse Event that is determined to be related, transforming it into an ADR, must be reported immediately, often within seven or fifteen days.

This distinction dictates the content of the drug label or Package Insert. The Adverse Reactions section of the label lists the side effects that the drug causes or is strongly suspected of causing. It does not list every negative health event that happened to patients during the trial. If the distinction between AE and ADR were not made, drug labels would be cluttered with random occurrences like broken bones and common colds

that happened by chance, making it impossible for patients and doctors to understand the true risks of the medication. Thus, the filter of causality the intellectual process of moving an event from AE to ADR is the essential mechanism that turns raw, noisy data into useful, actionable medical information.

SERIOUSNESS CRITERIA

(THE 6 CRITERIA FOR SAEs)

In the lexicon of drug safety, precise terminology is the difference between a routine data point and a regulatory emergency. One of the most persistent sources of confusion for students, patients, and even seasoned healthcare professionals is the distinction between "**severity**" and "**seriousness**." While these words are synonyms in everyday language, in pharmacovigilance, they represent two entirely different concepts.

Severity describes the intensity of a specific event (graded as mild, moderate, or severe). Seriousness, however, describes the outcome of the event or the threat it poses to the patient's life. To illustrate this, consider a patient who experiences a headache so intense they cannot leave their bed or open their eyes. This is clinically a "severe" headache, but unless the patient is admitted to the hospital or the event is caused by a brain hemorrhage, it is not "serious" in the regulatory sense. Conversely, a patient might suffer a "mild" stroke that results in a slight, permanent droop of the eyelid. The clinical intensity is mild, but because it resulted in a permanent disability, the event is classified as "serious." This distinction is paramount because only Serious Adverse Events (SAEs) trigger the rapid, expedited reporting timelines (7 or 15 days) to health authorities like the FDA and EMA.

END OF PREVIEW

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