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Professional Development Resources | **VIGILANCE**

What's Inside?

Introduction to Pharmacovigilance : Principles & Applications

SUMMARY

Poor product quality, adverse drug reactions (ADRs), and medication errors have a significant impact on healthcare systems, compromising patient care and driving up costs. While most data on these issues and the importance of pharmacovigilance come from developed countries, low- and middle-income countries likely face even greater challenges due to weaker health infrastructure, inconsistent medicine supply and quality, insufficiently trained healthcare staff, and limited access to communication and information technology.

Pharmacovigilance focuses on three main areas:

- Product Quality
- Adverse Drug Reactions (ADRs)
- Medication Errors

Health professionals often associate pharmacovigilance primarily with identifying and reporting unknown, serious ADRs linked to new medications. However, pharmacovigilance is integral to all stages of pharmaceutical management: selection, procurement, distribution, usage, management support, and policy and legal frameworks. It operates at facility, national, and international levels, requiring collaboration among diverse stakeholders with various responsibilities. National governments are tasked with ensuring that medicines within their borders are high-quality, safe, and effective, supported by a national pharmacovigilance system backed by drug regulatory authorities. Unfortunately, pharmacovigilance is not part of the legal framework in some countries. Certain public health initiatives, such as those for HIV/AIDS and malaria, may have distinct pharmacovigilance systems, while hospitals often implement facility-based medication safety programs.

Key components of a pharmacovigilance system include data collection - either passive, active, or mandatory - along with data analysis and reporting. When ADEs occur, they must be evaluated, reported, and communicated effectively to relevant stakeholders, including the national pharmacovigilance center (if available) and the World Health Organization's (WHO) International Drug Monitoring Programme. Based on these evaluations, corrective actions should be taken to mitigate adverse drug events and enhance patient care. Feedback on implemented interventions should be shared with data reporters to encourage ongoing engagement. Follow-up analysis can then assess the interventions' success.

The use of medicines is a balance between benefits and potential risks. Pharmacovigilance plays a critical role in minimizing harm by ensuring that high-quality medicines are used rationally.

1. What is Pharmacovigilance and Why is it important?

The World Health Organization (WHO) defines pharmacovigilance as "The science and activities related to the detection, assessment, understanding, and prevention of adverse effects or any other medicine-related problem" (WHO 2004). Terminology associated with pharmacovigilance can vary across different contexts and organizations, and the terms used here are outlined in **Table 1.1.**

Evidence increasingly reveals the significant impact of poor product quality, adverse drug reactions (ADRs), and medication errors on healthcare systems. However, estimating the full extent of these issues is challenging, as many cases go unreported. Available data, primarily from industrialized countries, highlight the scope of the problem. For instance, a landmark report by the U.S. Institute of Medicine (IOM) in 2000 estimated that medication errors and ADRs contribute to over 7,000 deaths annually, with associated hospital costs ranging between 17 and 29 billion USD per year. A later IOM report in 2006 found that more than 1.5 million Americans are injured each year by medication errors across hospitals, nursing homes, and doctors' offices. The consequences of these adverse drug events (ADEs) extend beyond cost, impacting patient trust in the healthcare system.

Table 1.1 : Definitions of terms related to Pharmacovigilance

Terms	Definition	Example
Harm occurred		
Adverse drug event	Harm caused by the use of a drug	Heart arrhythmia from discontinuing atenolol (whether or not it was considered an error)
Adverse drug reaction	Harm caused by the use of a drug at normal doses	Skin rash from Nevirapine
Harm may have occurred		
Medication error	Preventable event that may cause inappropriate use of a drug or use or patient harm	Failure to renew prednisone order on transfer to medical ward
Harm did not occur		
Potential adverse drug event	Circumstances that could result in ha rm by the use of a drug but did not harm the patient	Receipt of another patient's ampicillin, with no resulting effect

Source: Adapted from Nebeker, Barach, and Samore 2004.

In low- and middle-income countries, these issues may be more critical due to weaker healthcare infrastructure, unreliable medication quality, and a shortage of trained healthcare professionals.

Pharmacovigilance encompasses three main areas:

- Product Quality
- Adverse Drug Reactions (ADRs)
- Medication Errors

Quality concerns include pharmaceutical products that are defective, degraded, or compromised by poor manufacturing practices, improper storage, inadequate labeling, or tampering. Counterfeit products and medicines that lose potency when stored at high temperatures fall under this category. Additionally, pharmaceutical donations sometimes arrive close to expiration or stored under adverse conditions, which can affect their quality.

Adverse Drug Reactions (ADRs)

An adverse drug reaction (ADR) is an unintended and harmful response to a medication given correctly, according to its recommended dosage, frequency, route, and technique of administration. ADRs can include allergic responses, withdrawal effects, or interactions with other medications. The World Health Organization (WHO) defines a serious ADR as any reaction that is fatal, life-threatening, causes significant or permanent disability, requires or extends hospitalization, or relates to misuse or dependency (WHO/UMC 2000).

During the development of a new medicine, it undergoes rigorous testing in both animal and human trials to assess safety and efficacy. However, by the time a drug reaches the market, it has typically been tested on only a few thousand individuals far fewer than those who may eventually use it. As a result, the safety data gathered during premarketing studies may not fully represent the entire population of users, making postmarketing surveillance essential to completing a drug's safety and efficacy profile. (Ahmad 2003).

Postmarketing surveillance, involving a much larger and more diverse patient population, helps detect rare but severe ADRs, chronic toxicities, and specific effects on sensitive groups, such as children, pregnant women, and the elderly, as well as potential interactions with other drugs, herbal products, or foods. However, identifying a direct link between an ADR and a particular drug can be challenging, as ADRs may occur long after the drug was taken, complicating causality confirmation. See **Table 1.2** for methods to evaluate probable causation.

Medication Errors

The National Coordinating Council for Medication Error Reporting and Prevention defines a medication error as "any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is under the control of a healthcare professional, patient, or consumer" (source: http://www.nccmerp.org/aboutMedErrors.html). These errors can vary in severity, ranging from harmless to harmful for the patient.

These errors can vary in severity, ranging from harmless to harmful for the patient. A study involving thirty-six healthcare facilities across the United States found that nearly one in five medication doses was administered incorrectly, with 7% posing a risk of patient harm (Barker et al., 2002).

Table 1.2 : Determining ADR probability using indicators.

No	Probability scale: Indicators	Yes	No	Don't Know
1	Are there previous conclusive reports on this ADR?	+1	0	0
2	Did the ADR appear after the suspected drug was administered?	+2	−1	0
3	Did the ADR improve when the drug was discontinued or a specific antidote was administered?	+1	0	0
4	Did the ADR reappear when the drug was readministered?	+2	−1	0
5	Could alternative causes (other than the drug) have caused the ADR on their own?	−1	+2	0
6	Was the drug detected in the blood (or other fluids) in a concentration known to be toxic?	+1	0	0
7	Was the ADR more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0
8	Did the patient have a similar ADR to the same or similar drugs in any previous exposure?	+1	0	0
9	Did any objective evidence confirm the ADR?	+1	0	0
	Total score =	?		

Possible = 0 - 4 | Probable = 5 - 8 | Definite = >9

Source: Naranjo et al. 1981.

Medication errors often stem from flawed systems, processes, or environmental conditions that lead to mistakes or hinder their prevention. For instance, keeping concentrated, toxic solutions in hospital wards without proper dilution has led to fatal incidents. Other contributing factors include illegible handwriting, risky abbreviations, missed interactions with other medications, and verbal miscommunications due to sound-alike or look-alike products.

Medication errors should be preventable through better education and robust system controls involving pharmacists, prescribers, nurses, administrators, regulators, and patients.

Adverse drug events

An Adverse Drug Event (ADE) is a harmful reaction caused by a drug or the improper use of a drug. While an Adverse Drug Reaction (ADR) is always classified as an ADE, an ADE can also result from situations such as an overdose due to a dispensing error or another error in the medication use process. (**Figure 1.1**).

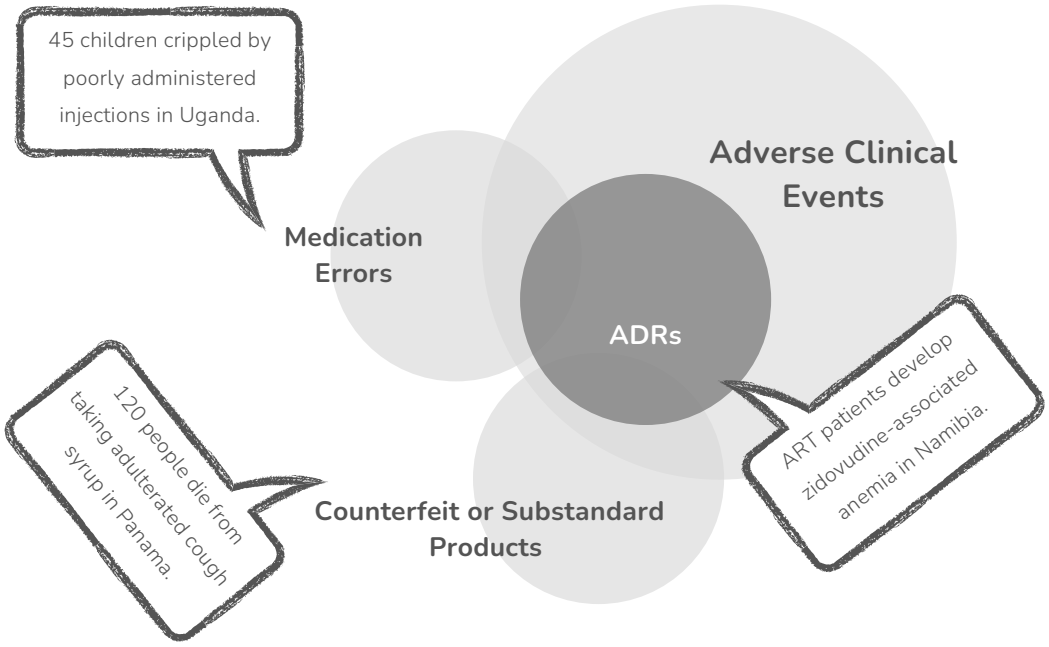


Fig 1.1: Relationship of medication safety terms

Sources: SPS 2009, figure 1, adapted from Barker et al. 2002; Ferner and Aronson 2006; Nebeker, Barach, and Samore 2004.

Patterns in medication use significantly affect ADE incidence. For instance, injectable medications, more frequently used in developing countries, are often associated with higher ADE rates (WHO/UMC 2002). Factors like self-medication, lack of regulatory oversight on medicine sales, and irrational prescribing also contribute to the prevalence of ADEs.

ADEs may be preventable, as in cases involving medication errors, or non-preventable, such as when they stem from unknown allergies. A potential ADE includes errors that do not harm the patient, like a dispensing error caught and corrected before reaching the patient. Documenting ADEs and ADRs is crucial, especially for new drugs, as post-marketing data can lead to updated usage guidelines, changes to packaging or labeling, or even product recalls. Recording potential ADEs is also valuable for identifying issues that could be addressed, such as communication gaps within a healthcare facility or medicines with similar names stored closely, which might lead to confusion.

2. WHO-UMC system for standardised case causality assessment

Rationale for Causality Assessment

A fundamental issue in pharmacovigilance is that most case reports pertain to suspected adverse drug reactions (ADRs), where diagnostic certainty is challenging. Adverse reactions are seldom specific to a drug, diagnostic tests are typically unavailable, and rechallenge, while informative, is rarely ethically feasible. As a result, ADR cases generally fall within an ambiguous spectrum between "certain" and "unlikely" — typically classified as "possible" or "probable." To address this ambiguity, numerous structured systems have been developed to assess causality in a standardized manner. However, none of these systems provides an exact and consistent quantitative likelihood of causality. Despite limitations, causality assessment is an established procedure in pharmacovigilance, as summarized in **Table 2.1.**

Table 2.1 : Advances and Limitations of standardised case causality assessment

What causality assessment can do?	What causality assessment cannot do?
Decrease disagreement between assessors	Give accurate quantitative measurement of relationship likelihood
Classify relationship likelihood	Distinguish valid from invalid cases
Mark individual case reports	Prove the connection between drug and event
Improvement of scientific evaluation; educational	Quantify the contribution of a drug to the development of an adverse event
-	Change uncertainty into certainty

The WHO-UMC Causality Assessment System

Developed in collaboration with national centers within the Programme for International Drug Monitoring, the WHO-UMC system serves as a practical tool for causality assessment. This system integrates clinical-pharmacological details of the case history with the quality of supporting documentation. Since pharmacovigilance focuses on identifying unknown or unexpected adverse reactions, prior knowledge and statistical probability are less emphasized within this framework. Notably, the definitions and their interpretation can be subjective, leading to variability in individual judgments. While some alternative algorithms exist, they are often too complex or narrowly tailored for broader applicability. The WHO-UMC system provides a structured approach to evaluate which causality category best fits a given case, as shown in **Table 2.2.**

Table 2.2 : WHO-UMC Causality Categories

Causality term	Assessment criteria*
Certain	• Event or laboratory test abnormality, with plausible time relationship to drug intake. • Cannot be explained by disease or other drugs. • Response to withdrawal plausible (pharmacologically, pathologically). • Event definitive pharmacologically or phenomenologically (i.e. an objective and specific medical disorder or a recognised pharmacological phenomenon). • Rechallenge satisfactory, if necessary.
Probable / Likely	• Event or laboratory test abnormality, with reasonable time relationship to drug intake. • Unlikely to be attributed to disease or other drugs. • Response to withdrawal clinically reasonable. • Rechallenge not required
Possible	• Event or laboratory test abnormality, with reasonable time relationship to drug intake. • Could also be explained by disease or other drugs. • Information on drug withdrawal may be lacking or unclear.
Unlikely	• Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible. • Disease or other drugs provide plausible explanations.
Conditional / Unclassified	• Event or laboratory test abnormality. • More data for proper assessment needed, or • Additional data under examination.
Unassessable / Unclassifiable	• Report suggesting an adverse reaction. • Cannot be judged because information is insufficient or contradictory. • Data cannot be supplemented or verified.

* All points should be reasonably complied with

Sources: The Uppsala Monitoring Centre

Use and Application of the WHO-UMC System

To understand how this system functions, it is useful to contrast the criteria for "Probable" and "Certain." The "Certain" category includes an additional criterion: "Event definitive pharmacologically or phenomenologically." This criterion requires the event to be a well-recognized medical condition or pharmacological phenomenon (e.g., grey baby syndrome due to chloramphenicol, or immediate anaphylaxis following re-exposure to a previously administered drug). This criterion restricts the "Certain" classification to events where other potential causes are ruled out. For "Certain" cases, information from rechallenge with a clear outcome is typically necessary, except in instances where the evidence is compelling without re-exposure. Conversely, for "Probable" cases, rechallenge information is not essential.

For "Certain" cases, the time interval between drug initiation and adverse event onset must be "plausible," with strong support indicating a causal link. In contrast, "Probable" cases only require a "reasonable" time relationship, a more neutral term that allows for some flexibility. Regarding alternative causes, "Certain" cases must lack any alternative explanations, while "Probable" cases only require the alternative cause to be "unlikely." Dechallenge outcomes also differ: a "Certain" classification necessitates a positive pharmacological or pathological argument implicating the drug, whereas for "Probable" cases, it suffices if the outcome is "clinically reasonable."

Differentiating Between Categories

The main distinctions between "Probable" and "Possible" relate to the presence of other plausible explanations or uncertainty about dechallenge outcomes. Cases are categorized as "Unlikely" if the timing is implausible or an alternative explanation is more probable. "Unclassified/Conditional" applies when more data are needed for proper assessment, whereas "Unclassifiable" is used when the report contains unresolvable inconsistencies or incomplete information.

In practice, "Possible" and "Probable" are the most frequently assigned categories. The typical approach involves selecting an initial category based on the case assessment, then adjusting to higher or lower categories as warranted by the case details. For drug-drug interactions, the WHO-UMC system assesses the "actor drug" that alters the pharmacokinetics or pharmacodynamics of another drug taken over a longer duration, considering the patient's medical context.

Practical Application and Case Examples

The WHO-UMC causality assessment system’s application will be illustrated through actual case reports, which will be accessible on the UMC website for practical reference.

Pharmacovigilance System in INDIA

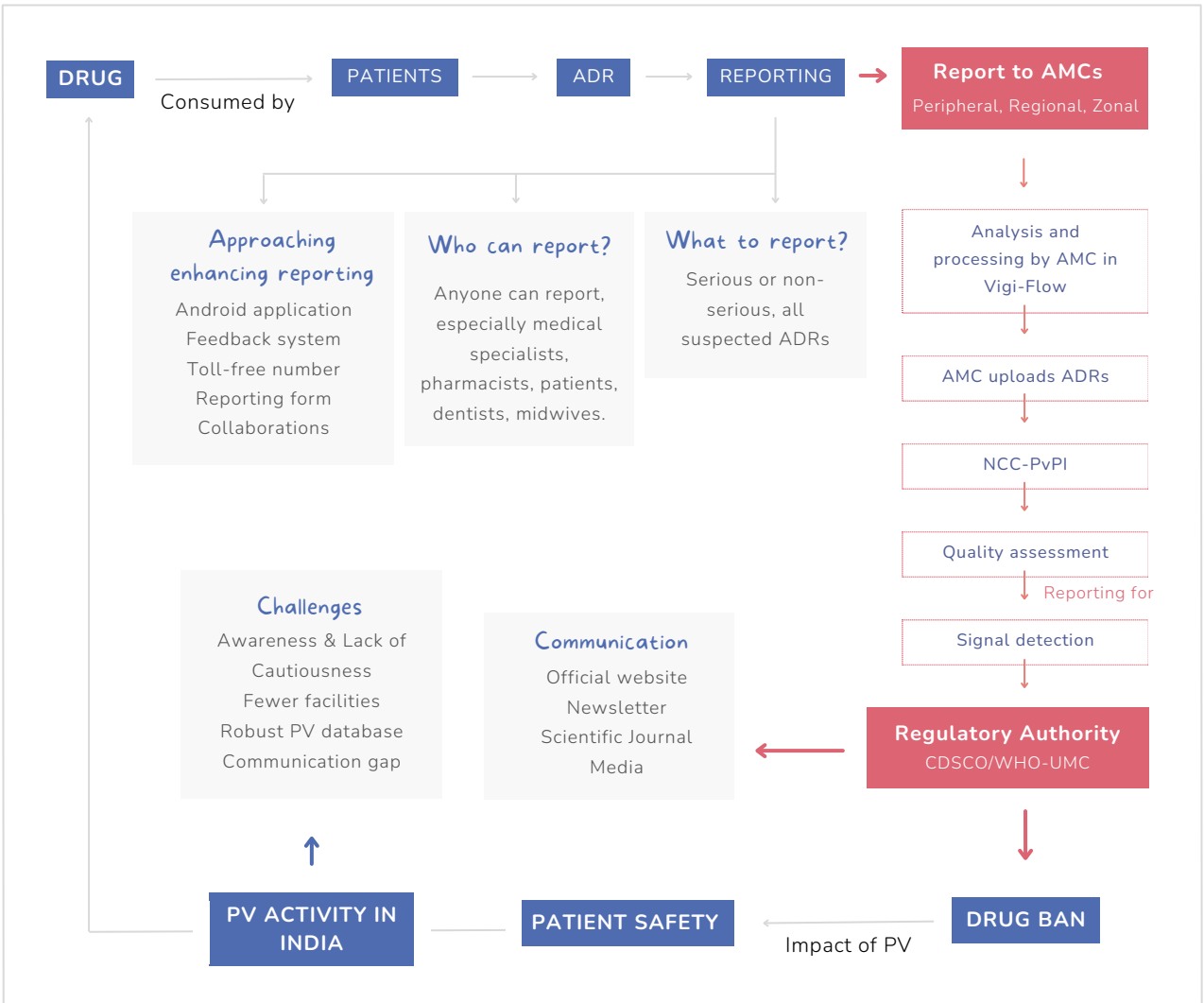
Pharmacovigilance in India has evolved over decades, driven by the critical need for drug safety monitoring and regulation. Emerging in the 1960s alongside India's pharmaceutical sector, formal efforts to address drug safety began in the 1980s and 1990s, led by the Indian Pharmacopoeia Commission (IPC), which pioneered adverse drug reaction (ADR) monitoring and established safety databases.

The early 2000s saw the heightened importance of pharmacovigilance due to globalization and rapid industry growth, which presented challenges in drug safety reporting and regulatory compliance. The Central Drugs Standard Control Organization (CDSCO) and IPC responded with initiatives to strengthen pharmacovigilance nationally.

In 2010, India joined the World Health Organization's Programme for International Drug Monitoring, enhancing global pharmacovigilance integration. This led to the establishment of the Pharmacovigilance Programme of India (PvPI), aimed at improving ADR monitoring, data analysis, and risk assessment.

PvPI created regional monitoring centers, strengthening reporting frameworks and fostering collaboration across healthcare professionals, industry, and consumers. Awareness initiatives have since increased among healthcare providers and the public.

Today, pharmacovigilance in India continues to advance with new regulations to improve drug safety monitoring, focusing on rigorous reporting, analysis, and information dissemination to safeguard patient health. As India's pharmaceutical industry expands, pharmacovigilance remains essential for public health, enhancing global healthcare by prioritizing drug safety.



3. Designing a Pharmacovigilance System

Health professionals often think of pharmacovigilance as identifying and reporting previously unknown or severe adverse drug events (ADEs) for new products. However, pharmacovigilance is integral to all stages of the pharmaceutical management cycle. **Figure 3.1** illustrates the connection between pharmacovigilance and pharmaceutical management.

While many national pharmacovigilance programs focus primarily on ADE reporting, a comprehensive approach should also address medication errors, therapeutic ineffectiveness (due to factors like low adherence, antimicrobial resistance, product quality issues, misuse, or drug interactions), product quality concerns, and effective communication of these insights to healthcare providers and consumers to aid in risk-benefit decision-making (SPS 2009). For instance, as pharmacovigilance systems advance, they may shift from relying solely on voluntary ADE reports from healthcare providers or consumers to active surveillance using registries, sentinel sites, and follow-up of defined patient groups to address key safety concerns. Expanding the system may also include linking quality assurance with adverse drug reaction (ADR) monitoring and establishing mechanisms to communicate medicine safety information to healthcare providers and the public.

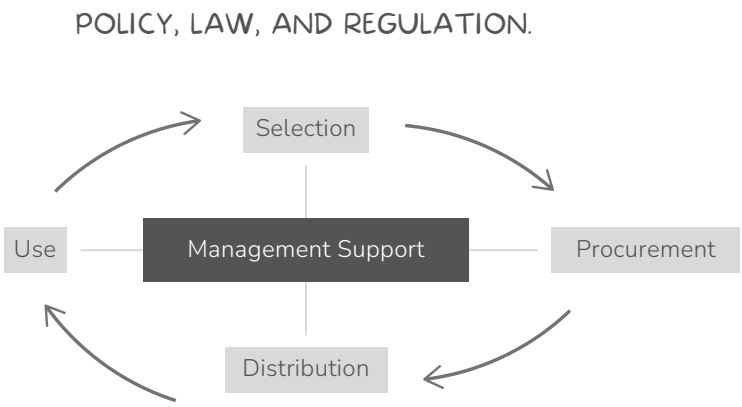


Fig 3.1: Relationship of medication safety terms.

A robust pharmacovigilance system involves resources and actions at facility, national, and international levels, promoting collaboration among diverse partners to ensure medicine safety. **Figure 3.2** outlines a comprehensive, ongoing pharmacovigilance system with components for monitoring, detecting, reporting, evaluating, and documenting safety data and providing feedback to prescribers, healthcare workers, and consumers. Collected information is analyzed by experts such as epidemiologists or pharmacologists to assess the adverse event's severity, likely causality, and preventability.

For the pharmacovigilance system to be effective, significant findings must be communicated to an entity with authority to take action, whether at a facility, national, or international level. This entity could be a hospital's drug and therapeutics committee, a national pharmacovigilance center, or the WHO Programme for International Drug Monitoring. The ultimate goal of a pharmacovigilance system is to reduce medicine-related problems, thereby lowering morbidity and mortality rates.

A pharmacovigilance system requires collaboration at facility, national, and international levels and involves various stakeholders, as summarized in **Table 3.1**. Key questions for designing such a system include determining if data flows will be separate or combined across pharmacovigilance areas, identifying responsibilities for data collection and reporting across health system levels, and deciding if pharmacovigilance will be integrated with or separate from public health programs. For example, at the facility level, the drug and therapeutics committee may oversee pharmacovigilance responsibilities. Additionally, pharmacovigilance data can guide formulary decisions, treatment guidelines, policy updates, and regulatory actions across various levels.

PV Activity	Detection within the pharmaceutical management framework	Prevention
Product Quality	• Most product quality issues in pharmaceuticals arise during the distribution phase. • Physical inspections are carried out when products are received from suppliers and at various points of distribution to ensure patient safety. • Efficacy complaints are often reported during product use.	• Prequalifying suppliers during procurement. • Implementing a robust pharmaceutical quality assurance program. • Developing a legal and policy framework that enforces pharmaceutical quality. • Enforcing laws and regulations related to product quality.
ADRs	• During use, adverse drug reactions (ADRs) are primarily detected through surveillance and monitoring systems.	• Incorporate ADR data into formulary decisions and standard treatment guidelines, and report ADRs to relevant facility, national, and international bodies. • Train health professionals on ADRs, and communicate effectively with patients about possible reactions.
Medication errors	• Errors can occur at any stage of the pharmaceutical management cycle, including ordering, storing, labeling, compounding, dispensing, transcribing, prescribing, administering, and monitoring.	Prevention strategies should address each process: • Promote a culture of safety with a non-punitive approach to error reporting. • Enhance access to comprehensive drug information. • Provide training and education to staff. • Consider historical and potential errors in product or formulary selection. • Issue prescribing guidelines. • Establish clear dispensing and administration procedures. • Implement monitoring protocols. • Improve communication, both written and oral. • Engage patients and their families in the care plan.

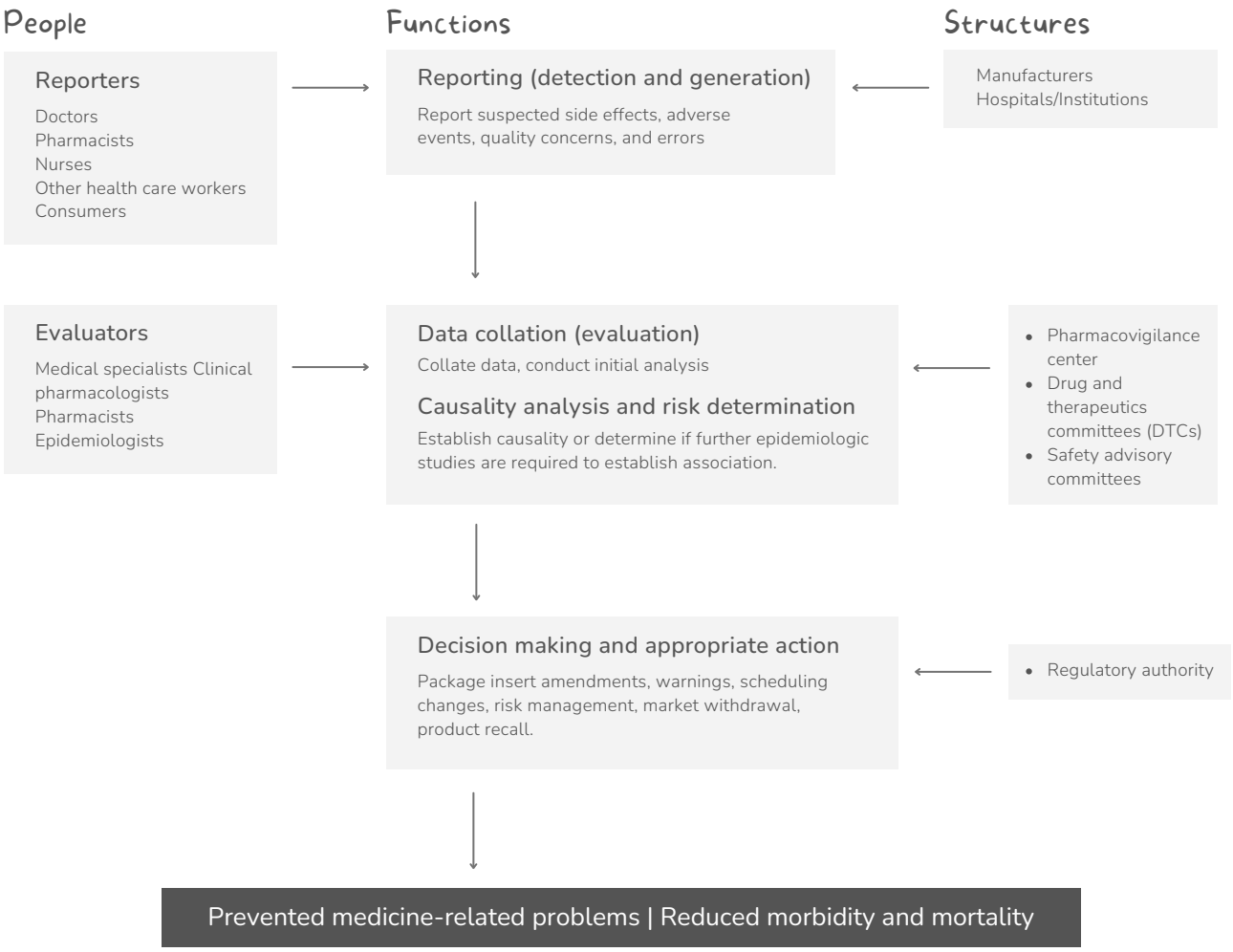


Fig 3.2: The Pharmacovigilance framework

Source: CPM/MSH 2011.

Pharmacovigilance activities at the facility level

Medication safety monitoring is a vital component of delivering high-quality healthcare, particularly in hospitals. Research from the U.S. indicates that adverse drug events (ADEs) among hospitalized patients lead to serious health and economic impacts (Classen et al., 1997). Within hospitals, monitoring and reporting medication errors and adverse drug reactions (ADRs) are essential parts of a robust safety system. Consequently, a significant amount of ADE data originates from hospitals due to both the heightened risks in these settings and the well-documented strategies for improvement. However, ADEs are also prevalent in other healthcare environments, including doctors' offices, nursing homes, pharmacies, and patients' homes, where underreporting remains a substantial issue.

Even in countries that lack a national pharmacovigilance infrastructure, hospitals are often equipped to develop and operate their own facility-based pharmacovigilance systems. These systems typically fall under the responsibility of the drug and therapeutics committee, focusing on safe medication practices and comprehensive pharmacovigilance.

Hospital-reported ADRs contribute significantly to clinical experience, advancing understanding in pharmacotherapy, while ADE assessments provide actionable insights to reduce medication errors and enhance patient care.

Pharmacovigilance activities at the national level

National governments play a critical role in ensuring that medicines available within their jurisdictions are of high quality, safe, and effective. A key element of a country's ability to oversee medication safety is the establishment of a national pharmacovigilance system, typically supported by the national drug regulatory authority.

National pharmacovigilance centers are responsible for

- Promoting the reporting of ADEs
- Collecting case reports of ADEs
- Clinically evaluating case reports
- Collating, analyzing, and evaluating patterns of ADEs
- Promoting policies and interventions that help prevent medication errors
- Determining what case reports constitute true adverse reactions to medications
- Recommending or taking regulatory action in response to findings supported by good evidence
- Initiating studies to investigate significant suspect reactions
- Alerting prescribers, manufacturers, and the public to new risks of adverse events
- Sharing their reports with the WHO Programme for International Drug Monitoring (WHO/UMC 2006)

A national pharmacovigilance system can be housed in a national pharmacovigilance center or a tertiary or research-oriented hospital. In the traditional model, a pharmacovigilance system was strongly centralized and consisted of one national center collecting reports from health professionals around the country. Many countries are moving toward a more decentralized system with a national center functioning as a focal point for regional or facility-based centers (WHO/UMC 2000).

Pharmacovigilance in Public Health Programs

Countries often have public health initiatives focused on specific diseases, such as HIV/AIDS, tuberculosis, malaria, and vaccination programs, which may operate independently from the primary healthcare system. These are known as vertical health programs, and they rely heavily on effective pharmacovigilance practices to ensure patient safety (WHO/UMC 2006). Monitoring adverse drug reactions (ADRs) is crucial, especially when expanding treatment access, like antiretroviral therapy (ART) for HIV/AIDS, or changing treatment guidelines, such as adopting artemisinin-based therapies for malaria.

The primary goals of pharmacovigilance in public health initiatives align with those of the national pharmacovigilance system. The structure of the national system typically informs the design of pharmacovigilance within public health programs.

In cases where no national pharmacovigilance system exists, public health programs may establish their own, potentially serving as a foundation for a future national system. For instance, Kenya's Ministry of Health incorporated pharmacovigilance responsibilities as ART programs expanded and facility-based ADR monitoring systems were developed, exemplifying a bottom-up approach.

The WHO provides comprehensive resources on pharmacovigilance as a tool in public health treatment programs (WHO/UMC 2006).

Table 2.1: Roles and responsibilities of partners in pharmacovigilance

Partner	Responsibilities
Government	• Establish national pharmacovigilance system. • Develop regulations for medicine monitoring. • Provide up-to-date information on adverse reactions to professionals and consumers. • Monitor effect of pharmacovigilance through indicators and outcomes.
Industry	• Provide quality medicines of assured safety and efficacy. • Assess and share ADRs that are reported.
Hospitals	• Promote the incorporation of pharmacovigilance into procedures and clinical practice.
Academia	• Teach, train, conduct research, and develop policy about pharmacovigilance. • Include pharmacovigilance in curriculum.
Medical & pharmaceutical professional associations	• Provide training and awareness to health professionals regarding pharmacovigilance.
Poisons and medicines information centers	• Provide information on medication safety and pharmacovigilance. • Collaborate with national pharmacovigilance centers, if applicable.
Health professionals (including physicians, nurses, pharmacists, dentists)	• Detect, investigate, manage, and report ADRs, medication errors, and product quality concerns. • Counsel patients about ADRs.
Patients and consumers	• Understand to the extent possible their own health problems and participate in the treatment plan by following medication instructions. • Report adverse reactions to health professionals as well as concomitant use of other medications, including traditional medicine.
Media	• Create awareness in the community about the safe use of medicines.

Pharmacovigilance Activities on the International Stage

Globalization, free trade, and internet access are transforming how people acquire and use medicines, highlighting the need for more interconnected pharmacovigilance efforts worldwide (WHO 2004). In response, WHO launched the Programme for International Drug Monitoring in 1968, initially involving ten countries. Today, with support from the Uppsala Monitoring Centre (UMC), the WHO program collaborates with national pharmacovigilance programs in nearly 100 countries (UMC 2010). The Uppsala Centre houses one of the largest databases of ADR reports, containing over five million case reports, and has established standardized reporting protocols to enhance international communication on medicine safety.

The Institute for Safe Medication Practices (ISMP) provides a global platform for healthcare providers and consumers to report adverse drug events (ADEs) confidentially. Although initially designed for U.S.-based reporting, ISMP accepts submissions from any country. After removing personal identifiers, reports are shared with the U.S. FDA, manufacturers, and others to address issues in drug labeling, packaging, and naming that could lead to errors.

Key components of a pharmacovigilance system include data collection—either voluntary or mandatory—alongside data analysis and reporting.

4. Data Collection

Passive Data Collection

Passive reporting of adverse drug reactions (ADRs) and medication errors, commonly known as voluntary or spontaneous case reporting, requires active engagement from healthcare providers to foster a culture of safety. Programs solely dependent on voluntary reporting capture only a limited scope of medication events, with calculated rates often reflecting reporting frequency rather than true event incidence. Nevertheless, voluntary reporting is essential, as it promotes a team-based approach to patient care improvement and risk reduction.

Challenges in voluntary reporting include:

- Fear of punitive action from supervisors or colleagues (in cases of errors)
- Fear of legal liability for the provider or facility
- Inability to recognise that an incident has occurred
- Ambiguity or complexity in the reporting process
- Limited improvement responses from institutions
- Lack of time

The primary aim of an effective monitoring system is to learn from and rectify error sources rather than penalise individuals. To address this, institutions should not only encourage voluntary reporting but also implement educational programs that emphasise the benefits of reporting, highlighting the improvements resulting from reported events.

Mandatory Data Collection

In many countries, pharmaceutical manufacturers and distributors are legally obligated to report ADR data collected during postmarketing surveillance to regulatory authorities. Additionally, healthcare facilities pursuing accreditation are often required to maintain an adverse drug event (ADE) reporting system as part of their compliance process. Some nations mandate ADE reporting by healthcare professionals, though the effectiveness of such legislative measures remains uncertain (WHO/UMC 2000).

Active Data Collection

Active data collection, conducted as a structured activity, encompasses methods like trigger tools, patient chart audits, and direct observation. These approaches provide more reliable estimates of medication event occurrence rates and reveal trend data.

Trigger Tools

These tools identify potential ADRs by alerting users to specific orders, laboratory values, or clinical conditions. For instance, laboratory triggers might include abnormal parameters (e.g., serum glucose <50 mg/dL, white blood cell count <3000, or toxic drug levels) indicating a possible ADR.

Medication order triggers may include antidotes or reversal agents (e.g., Dextrose, Naloxone, Epinephrine) or sudden medication changes (e.g., Discontinuation of Digoxin). Clinical triggers may include conditions often associated with ADRs, such as rash, falls, or apnea. Studies suggest that combined triggers, such as laboratory results paired with medication orders, yield higher data accuracy (Schiff et al., 2003).

Chart Review

This process involves scrutinizing patient charts to identify ADRs, drug interactions, and medication errors, which can be conducted prospectively, concurrently, or retrospectively. Prospective reviews focus on recording adverse events in real-time, while retrospective reviews allow for convenience in data collection, though they may hinder in-depth analysis. For instance, the Ghana National Centre for Pharmacovigilance employs a straightforward ADR reporting form to document adverse reactions in pregnant patients (Dodoo, 2005), highlighting the value of prospective and concurrent reviews in preventing patient harm.

Direct Observation

Direct observation of medication administration offers valuable insights into the medication-use process, often identifying critical weaknesses. Observers may shadow nursing staff as they administer medications, recording discrepancies between physician orders and observed practices. This approach provides reliable error rates that inform targeted improvement measures. Research indicates that direct observation surpasses chart reviews and voluntary reporting in detecting medication errors (Flynn et al., 2002).

An example follows of the steps that could comprise data collection using direct observation of the medication administration process

1. The observer follows randomly selected nurses as they administer medications to patients on a hospital ward. The observer collects data for a specified number of medications using preprinted forms. **Figure 4.1** shows an example of an observation audit tool.
2. The observer verifies each medication on the original physician order in the patient chart, noting discrepancies between the written order and the actual practice observed in terms of medication, dose, frequency, route, and so on.
3. The data are used to calculate error rates for a specific focus area, such as the ward or the facility. Rates or trends may help identify problematic procedures or areas for additional training.

Data Collection Tools

Standardized forms facilitate ADR and medication error data collection, ensuring consistency and efficiency. Ideally, forms should align with national pharmacovigilance standards to harmonize data across healthcare settings. For ADR data, it is crucial to capture patient-specific information, including concurrent therapies, the patient's reaction, and the suspected medication's details. WHO offers guidelines on data form content for ADR monitoring (WHO 2002). In contrast, for medication error data, forms should capture information for system-wide analysis, identifying areas for improvement.

Figure 4.1 : Nonvoluntary data collection tool for pharmacovigilance

Source: Feinberg 2001.

MAR = medication administration record.

MEDICATION ADMINISTRATION AUDIT TOOL

Date and Time of Audit: _____ Department: _____

Name of the Evaluator: _____

Checklist for medication administration	Patient #1		Patient #2		Comments
	Yes	No	Yes	No	
1. Washes hands before start of medication administration process, before and after each patient contact, and before preparing injectable medications.					
2. Performs and charts necessary pre-administration assessments for specific medicines (pulse, blood pressure, nausea, etc.).					
3. Notes allergies and compares to medicines to be administered.					
4. Correctly identifies patient. Compares name and/or ID# on MAR with patient ID band. Cannot use room number for identification.					
5. Correct medication (removes medications and verifies correct medication with the MAR).					
6. Correct dosage (including accurate measurement of liquids).					
7. Correct route of administration.					
8. Correct time of administration (administers within 1 hour before or after time ordered; considers relationship to meals and/or food; waits appropriate time between ophthalmic medicines, inhaled doses, etc.).					
9. Explains purpose of each medication; answers questions about the medication.					
10. Stays with patient until each medication has been safely swallowed.					
11. Properly administers medications (preps IV port, appropriate IV compatibility, administers over correct time interval).					
12. After medication administration, initials time of administration for each medication and signs appropriate document.					
13. Correct disposal of pharmaceutical waste; disposes of narcotics and dangerous drugs with applicable documentation.					
14. Maintains the security of the medications at all times (locked medicine cabinet or locked medication room door).					

5. Data analysis and Reporting

Once Adverse Drug Reaction (ADR) data are gathered, thorough analysis is essential to evaluate the severity, probable causality, and preventability of each incident. Rigorous classification systems and algorithms have been developed for standardized assessment, facilitating accurate and actionable insights.

Severity *(impact on the patient's health)*: **Table 5.1** shows a classification for determining the severity of ADRs. It addresses both ADEs associated with medication error and those not associated with error, so it can be applied to all medication events.

Probable causality *(the likelihood that the medicine's use or lack of use contributed to the ADR)*: **Table 1.2** illustrates how to calculate the Naranjo Probability Score, a common method for determining whether a particular medicine was related to the ADR.

Preventability *(Was an error associated with the event?)*: **Box 5.1** is an algorithm used to help determine if the ADE was caused by a medication prescribing error, and therefore, preventable.

For ADRs identified as preventable, an in-depth analysis of system breakdown points is necessary. Recognizing where primary errors occur provides insights into specific vulnerabilities within healthcare processes. This may involve examining critical phases such as prescribing practices, medication types (e.g., injectables), patient demographics (e.g., elderly or pediatric patients), and operational factors such as staff experience (e.g., new employees or interns), clinical settings (e.g., high-risk areas like surgery or ICU), and timing (e.g., night shifts where errors may be more prevalent). For instance, if data reveal frequent errors involving incorrect dosages of injectable medications administered by nursing staff, focused corrective actions could include targeted training sessions, increased supervision, and the implementation of procedural changes, such as independent double-checks for all injectable doses. Tracking subsequent error rates post-intervention is key to evaluating improvement and making further adjustments if necessary.

Data Organization and Reporting

Organizing medication event data systematically, either through manual or electronic spreadsheets, is essential to facilitate comprehensive analysis. This structured data repository allows for efficient summarization and categorization, enabling detailed reporting both within the institution and across larger regions. National and international organizations often utilize internet-based ADR or medication error databases, which provide centralized platforms for aggregating data and sharing findings. Such databases support global efforts to identify trends, compare data across diverse healthcare settings, and establish benchmarks that contribute to safer medication practices worldwide (refer to References and Further Readings for additional resources).

Reporting to National Programs and Manufacturers:

To enhance drug safety knowledge on a broader scale, ADRs should be reported to the national ADR program, where available, and to the pharmaceutical manufacturer.

Table 5.1: Severity index for medication errors

Category	Description
Category A	Circumstances or events that have the capacity to cause error (note that these are potential, not actual, errors).
Category B	An error occurred but the error did not reach the patient (an "error of omission" does reach the patient).
Category C	An error occurred that reached the patient but did not cause patient harm.
Category D	An error occurred that reached the patient and required monitoring to confirm that it resulted in no harm to the patient or required intervention to preclude harm.
Category E	An event occurred that may have contributed to or resulted in temporary harm to the patient and required intervention.
Category F	An event occurred that may have contributed to or resulted in temporary harm to the patient and required initial or prolonged hospitalization.
Category G	An event occurred that may have contributed to or resulted in permanent patient harm.
Category H	An event occurred that required intervention necessary to sustain life.
Category I	An event occurred that may have contributed to or resulted in the patient's death.

Source: NCC MERP n.d.

Box 5.1 : Determining whether a medication error occurred

- Was the drug involved appropriate for the patient's clinical condition? (NO = Preventable)
- Was the dose, route, or frequency of administration appropriate for the patient's age, weight, or disease state? (NO = Preventable)
- Was required therapeutic pharmaceutical monitor- ing or other necessary laboratory tests performed? (NO = Preventable)
- Was there a history of allergy or previous events to the drug? (YES = Preventable)
- Was an interaction (medicine–medicine; medicine– food; medicine–herbal) involved in the ADR? (YES = Preventable)
- Was a toxic serum drug concentration (or laboratory monitoring test) documented? (YES = Preventable)
- Was poor compliance involved in the ADR? (YES = Preventable)
- Was the error considered preventable because of deviations in procedures or standards of practice? (Yes = Preventable)

Source: Adapted from Schumock and Thornton 1992.

6. Taking actions for Improvement

When adverse drug events (ADEs) occur, it is critical to analyze, report, and communicate their significance effectively to an informed audience capable of interpreting the information. Properly reported ADEs can drive national or even international responses, such as:

- Pharmaceutical manufacturers issuing "Dear Doctor" letters to inform healthcare providers of newly identified adverse reactions.
- Updates to medication package inserts by pharmaceutical manufacturers to reflect new safety information.
- Recalls of medications by manufacturers or national regulatory authorities in response to significant safety concerns.

At the clinical level, measures for managing serious or recurring ADEs may include:

- Revising the medication formulary if necessary.
- Implementing new prescribing protocols.
- Modifying dispensing procedures.
- Enhancing patient-monitoring practices.
- Providing staff education through face-to-face sessions, in-service training, bulletins, and reports on collected adverse drug reactions (ADRs).
- Educating patients on medication safety.

Most importantly, clinical actions should aim to foster a culture of safety within healthcare organizations to improve medication safety and reduce medication-related incidents. This commitment to safety, as outlined in **Box 6.1**, should be evident at all levels of leadership, with a focus on prioritizing safety over production or efficiency. Job descriptions and performance evaluations should include participation in safety initiatives supported by adequate resources, rewards, and incentives, while problem responses should prioritize system-wide improvements.

The Institute of Medicine (IOM, 2006) has emphasized the importance of doctors, nurses, pharmacists, and other healthcare providers discussing with patients the risks, contraindications, and possible adverse effects of medications, as well as advising on what to do if they experience an ADE. Patients should also be encouraged to engage actively in their own healthcare and be allowed sufficient time to consult with providers regarding their medications (also see the WHO patient safety initiative: http://www.who.int/patientsafety/en).

In summary, the therapeutic use of medications necessitates a balance between benefits and the potential for harm. Pharmacovigilance plays a key role in minimizing harm by ensuring high-quality, rational medicine use while addressing patient concerns and expectations in therapeutic decision-making. According to WHO (2004), achieving these goals involves:

- Supporting public health and fostering patient trust in medications and healthcare services.
- Anticipating and managing medication-related risks.
- Providing regulators with information necessary to update medicine use recommendations.
- Enhancing communication between healthcare professionals and the public.
- Educating healthcare providers on the efficacy and risks of the medications they prescribe.

Box 6.1 : Safe medication practices

- **Promote ADR Reporting:** Actively encourage staff to report adverse drug reactions, errors, and any unsafe alternatives to improve patient safety.
- **Use Clear Naming Conventions:** Emphasize using generic or brand names based on context to reduce confusion between similar-sounding products.
- **Participatory Culture:** Transition from a punitive safety culture to a participatory one, encouraging open communication and shared responsibility.
- **Standardized Medication Labeling:** Ensure that all medications are labeled consistently according to hospital policy, reducing variation and error.
- **Create a List of Unsafe Abbreviations:** Standardize abbreviations and compile a list of dangerous ones to avoid, including acronyms and symbols prone to misinterpretation.
- **Ensure Legible Documentation**: Require that all handwritten or printed orders are clear and legible to prevent misinterpretation.
- **Review Medication Orders Thoroughly**: Conduct a thorough review of medication orders for clinical appropriateness before dispensing and administration.
- **Clarify Ambiguous Orders:** Require clarification for any unclear orders or those that appear inconsistent with the patient's clinical condition.
- **Provide Access to Drug Information:** Ensure healthcare providers have easy access to reliable drug information to support safe prescribing and administration.
- **Implement Verbal Order "Read-Back" Protocols:** Confirm all verbal and telephone orders by reading back to verify accuracy.
- **Identify and Separate Look-Alike Products:** Recognize look-alike and sound-alike medications, and physically separate their storage to minimize mix-ups.
- **Label Patient-Specific Medications Clearly:** Dispense medications with patient-specific labels, and when possible, in a ready-to-administer form.
- **Follow the Five "Rights" of Administration:** Adhere to the rights of drug administration: right patient, right drug, right time, right dose, and right route.
- **Verify Patient Identity Consistently:** Cross-check patient identification with medication labels and orders prior to every administration.
- **Focus on High-Risk Medications:** Identify high-risk or problem-prone medications and implement tailored strategies to mitigate associated risks.
- **Limit Drug Concentration Variability:** Standardize or restrict the number of available drug concentrations to avoid dosing errors.
- **Remove High-Risk Medications from General Access:** Remove concentrated high-risk medications (e.g., electrolytes) from general patient care areas when feasible.
- **Engage Patients in Their Care:** Involve patients by informing them about each medication's name and purpose prior to administration to build understanding and awareness.
- **Educate on Medication Safety Standards:** Provide ongoing education and resources on safe medication practices to staff, aligning with best practices and policies.
- **Monitor and Evaluate Medication Safety Interventions:** Regularly assess the effectiveness of safety interventions and protocols, making adjustments as needed to maintain high standards.

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