CHAPTER 35

Pharmacovigilance

SUMMARY

Poor product quality, adverse drug reactions (ADRs), and medication errors greatly influence health care systems by negatively affecting patient care and increasing costs. Most of the statistics documenting the issues and highlighting the importance of pharmacovigilance come from developed countries, therefore low- and middle-income countries likely have greater problems because of the poorer state of their health system infrastructure, the unreliable supply and quality of medicines, the lack of adequately trained essential health care staff, and their limited access to communication and information technology.

Three areas of pharmacovigilance include—

- Product quality
- Adverse drug reactions
- Medication errors

Product quality problem reporting systems are covered in Chapter 19 on quality assurance. This chapter focuses on the importance of ADRs and medication errors and actions to take to minimize their impact. An ADR is a harmful response caused by the medicine after the patient has received it in the recommended manner; whereas, adverse drug events (ADEs) result from either the medicine itself or the medicine's inappropriate use or medication error.

Health professionals may still think of pharmacovigilance strictly in terms of identifying and reporting previously unknown and serious ADRs related to new products; however, pharmacovigilance activities are related to every sector of the pharmaceutical management framework: selection, procurement, distribution, use, management support, and the overarching policy and legal framework. Likewise, pharmacovigilance activities are carried out at the facility, national, and international levels and require collaboration among a wide range of partners with differing responsibilities. National governments are responsible for ensuring that medicines sold in their countries are of good quality, safe, and effective. An important component of a country's ability to monitor pharmaceutical safety is a national pharmacovigilance system that is supported by the drug regulatory authority. However, some countries have not included pharmacovigilance as part of their legal framework. Public health programs, such as those for treating HIV/AIDS and malaria, may have separate pharmacovigilance systems, while hospitals usually have the capacity to design and implement facility-based medication safety activities.

The major components of a pharmacovigilance system are data collection, which can be passive, active, or mandatory, and data analysis and reporting. When ADEs occur, they must be analyzed and reported and their significance must be communicated effectively to an audience that has the knowledge to interpret the information, including the national pharmacovigilance center, if one exists, and the World Health Organization (WHO) Programme for International Drug Monitoring. Based on the results of the analysis, actions should be carried out to reduce adverse drug events and thereby improve patient care. To encourage continued participation in the process, interventions should be shared with the data reporters. Follow-up data collection and analysis can then measure the effectiveness of the interventions.

The use of medicines involves a trade-off between benefits and the potential for harm. Pharmacovigilance can help minimize harm by ensuring that medicines of good quality are used rationally.

35.1 What is pharmacovigilance and why is it important?

WHO defines pharmacovigilance as "the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine-related problem" (WHO 2004, 1). Terms related to the science of pharmacovigilance are defined differently in different settings and by different organizations. The terms used in this chapter are defined in Table 35-1.

More and more evidence is showing the huge effect of poor product quality, ADRs, and medication errors on health care, but estimating the actual scale of this effect is almost impossible because most cases go undetected. Much of the documented evidence available on medicine quality and ADEs comes from industrialized countries. For example, in a bellwether report, the U.S. Institute of Medicine (IOM 2000) estimated that 7,000 or more people die each year from medication errors and ADRs and that the total costs may be between 17 billion U.S. dollars (USD) and USD 29 billion per year in hospitals nationwide. A follow-up report estimated that more than 1.5 million Americans are injured every year by medication errors in hospitals, nursing homes, and doctor's offices (IOM 2006). ADEs also are costly in terms of loss of trust in the health care system by patients.

Table 35-1 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 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 harm 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.

Compared with that in high-income countries, the situation in low-and middle-income countries is likely more urgent because of the poorer state of health system infrastructure, the unreliable supply and quality of medicines, and the lack of adequately trained essential health care staff.

Three areas of pharmacovigilance include—

- Product quality
- Adverse drug reactions
- Medication errors

Quality issues relate to pharmaceutical products that are defective, deteriorated, or adulterated because of poor manufacturing practices, inadequate distribution and storage, poor labeling, or tampering. Counterfeit products would fall under this category, for example, as would medicines that have lost their potency after being stored at high temperatures. These quality assurance issues, including product problem reporting systems, are covered in detail in Chapter 19. In addition, pharmaceutical donations have sometimes expired or are close to expiration or have been stored under conditions that adversely affect their quality. See Chapter 15 for more information about ensuring the quality of medicine donations.

This chapter focuses on the importance of ADRs and medication errors and actions to take to minimize them.

Adverse drug reactions

An ADR is a harmful response in the patient caused by the drug itself given in the recommended manner (dose, frequency, route, administration technique). Examples include allergic reactions, effects from withdrawal, or reactions caused by interactions with other medications. WHO defines a serious ADR as any reaction that is fatal, life-threatening, or permanently or significantly disabling; requires or prolongs hospitalization; or relates to misuse or dependence (WHO/UMC 2000).

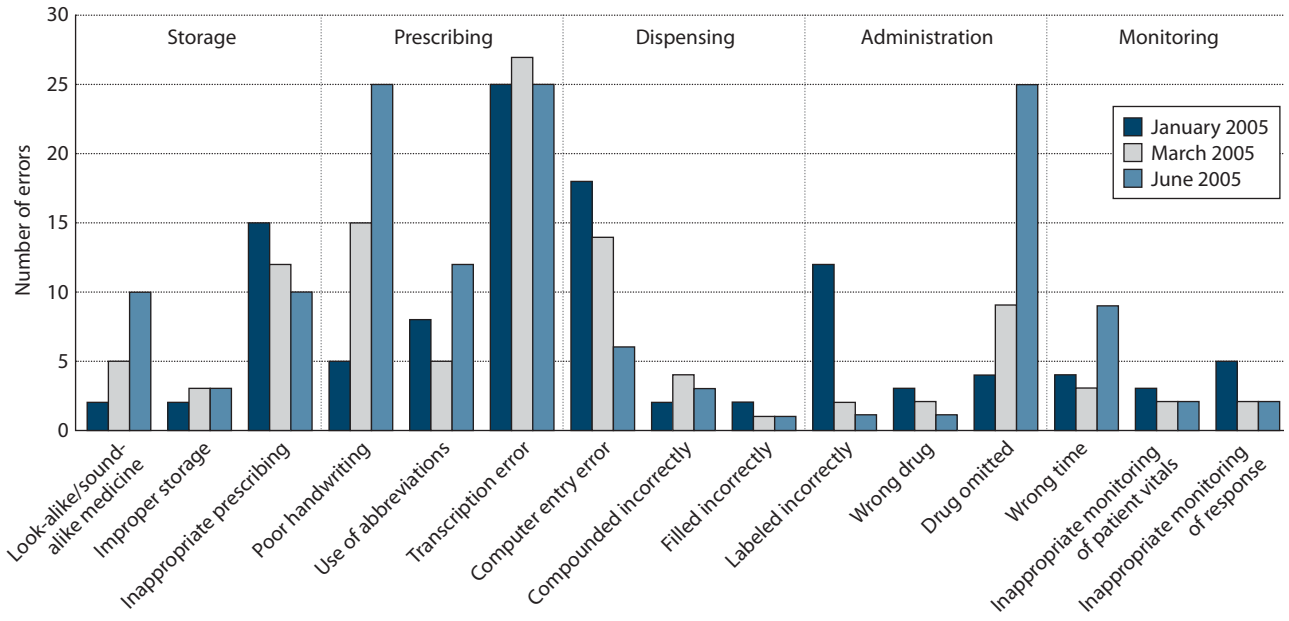
When a new medicine is being developed, it goes through several phases of testing, first with animals, then with human

Table 35-2 Determining ADR probability using indicators

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.

Figure 35-1 Analysis of medication errors in a U.S. hospital, 2005



Source: Chris Olson, unpublished data.

volunteers, for safety and efficacy. However, when a product is approved, it may have been tested in only thousands of patients—many fewer than are likely to use the product once it is approved for sale on the market. Therefore, the information on effects generated in premarketing studies is incomplete relative to the full complement of likely users, making postmarketing surveillance an important tool for completing the safety and efficacy profile of a drug product (Ahmad 2003).

Because it includes so many more people than are included in the premarketing surveillance process, postmarketing surveillance should be able to detect rare but serious adverse reactions; chronic toxicity; effects in sensitive groups, such as children, pregnant women, and the elderly; and interactions with other pharmaceuticals, herbal medicines, or food. Often, however, linking an ADR with a specific medicine is difficult; for example, an ADR can occur long after a medication is administered, which makes confirming the cause a challenge. See Table 35-2 for ways to analyze probable causality.

Box 35-1
Medication error caused by sound-alike products

Nurses and pharmacists at a hospital reported two cases where RECOMBIVAX HB (hepatitis B vaccine, recombinant) was given to newborns instead of Comvax (hemophilus B conjugate vaccine with hepatitis B vaccine). When a telephone order was misunderstood, the wrong product was administered to the patients. Nurses in the unit felt this same error had probably occurred other times without anyone noticing. A safe medication practice to prevent sound-alike product name errors is to transcribe and read back verbal orders. Face-to-face verbal orders should be accepted only in emergencies or when the prescriber is physically unable to write the order.

Source: ISMP 2003.

Medication errors

The National Coordinating Council for Medication Error Reporting and Prevention defines medication error as "any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer" (http://www.nccmerp.org/aboutMedErrors.html). Errors can be harmless or detrimental to the patient. A study of thirty-six health care facilities in the United States showed that nearly one in five doses of medication was given in error, and 7 percent had the potential to cause patient harm (Barker et al. 2002).

Medication errors are caused by faulty systems, processes, and conditions that lead people to make mistakes or fail to prevent mistakes (Figure 35-1). For example, stocking wards in hospitals with certain concentrated solutions, even

Table 35-3 Dangerous abbreviations

Abbreviation	Intended meaning	Common error	Preferred term
U	Units	Mistaken as a 0 (zero) or a 4 (four), resulting in overdose. Also mistaken for cc (cubic centimeters) when poorly written.	Write *unit*.
µg	Micrograms	Mistaken for mg (milligrams), resulting in a one-thousand-fold overdose.	Write *mcg*.
Q.D.	Latin abbreviation for every day	The period after the Q has sometimes been mistaken for an I, and the drug has been given QID (four times daily) rather than daily.	Write *daily*.
Q.O.D.	Latin abbreviation for every other day	Misinterpreted as QD (daily) or QID (four times daily). If the O is poorly written, it looks like a period or an I.	Write *every other day.*
SC or SQ	Subcutaneous	Mistaken as SL (sublingual) when poorly written.	Write *subcutaneous* or *subcut.*
T I W	Three times a week	Misinterpreted as three times a day or twice a week.	Write specific days for administration, for example, MON., WED., and FRI.
D/C	Discharge; also discontinue	Patient's medications have been prematurely discontinued when D/C (intended to mean discharge) was misinterpreted as discontinue, because it was followed by a list of drugs.	Write *discharge* or *discontinue.*
HS	Half strength	Misinterpreted as the Latin abbreviation HS (hour of sleep).	Write *half strength.*
cc	Cubic centimeters	Mistaken as U (units) when poorly written.	Write *ml* or *mL* or *mls* for milliliters.
AU, AS, AD	Latin abbreviation for both ears; left ear; right ear	Misinterpreted as the Latin abbreviation OU (both eyes); OS (left eye); OD (right eye).	Write *ear*.
Lack of a leading zero (.X mg) or Use of a trailing zero (X.0 mg)		Decimal point is missed, resulting in a dosage error of tenfold or greater.	Always lead with a zero before a decimal point (0.X mg). Never follow a whole number with a decimal point and zero (X mg).
@	at	Mistaken as zero.	Write *at*.
MS, MSO4 MgSO4	Morphine sulfate, magnesium sulfate	Confused for each other.	Write *morphine sulfate* or *magnesium sulfate.*
IU	International Unit	Mistaken as IV (intravenous) or 10 (ten).	Write *international unit.*

Source: http://www.nccmerp.org/dangerousAbbrev.html.

though they are toxic unless diluted, has resulted in deadly errors. Other problems can result from illegible handwriting, use of dangerous abbreviations (Table 35-3), overlooked interactions with other medicines, and verbal miscommunications and sound-alike or look-alike products. Box 35-1 describes a case where the wrong medicine was administered to babies because of a misunderstood verbal order.

Medication errors, by definition, should be preventable through education and effective systems controls involving pharmacists, prescribers, nurses, administrators, regulators, and patients.

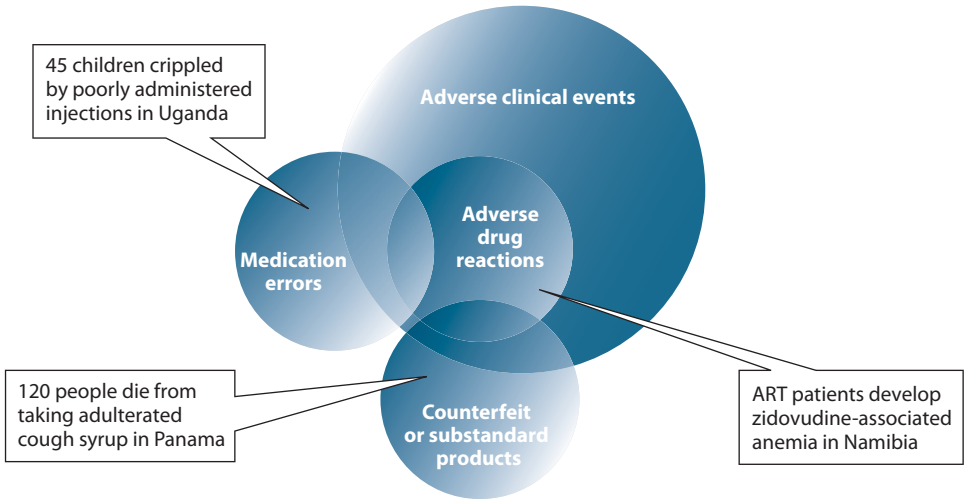
Adverse drug events

An ADE is a harmful response that is caused by a drug or the inappropriate use of a drug. Therefore, an ADR is always an ADE, but an ADE might include the result of an overdose because of a dispensing error or some other error occurring during the medication-use process. (See Figure 35-2.)

Medication-usage patterns strongly influence the incidence of ADEs. For example, injectable medications are more commonly used in developing countries, and they are more likely to be associated with ADEs (WHO/UMC 2002). In addition, self-medication, lack of regulatory control over the sale of medicines, and irrational prescribing all contribute to the incidence of ADEs.

ADEs are preventable when they are the result of a medication error (discussed below) or nonpreventable, as would be the result of an unknown allergy. A potential ADE could include an error that may or may not reach the patient but does not cause harm, such as a dispensing error that was discovered and avoided at the last minute. The documentation

Figure 35-2 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.

of ADEs and ADRs is important—especially in new products—where such postmarketing information can result in changes to the recommended usage, product packaging or labeling, or even a recall. Identifying and documenting potential ADEs is useful because this can identify problem areas that might be corrected, such as a communication problem within the health facility or two medicines with similar names being stored next to and therefore confused with each other.

35.2 Designing a pharmacovigilance system

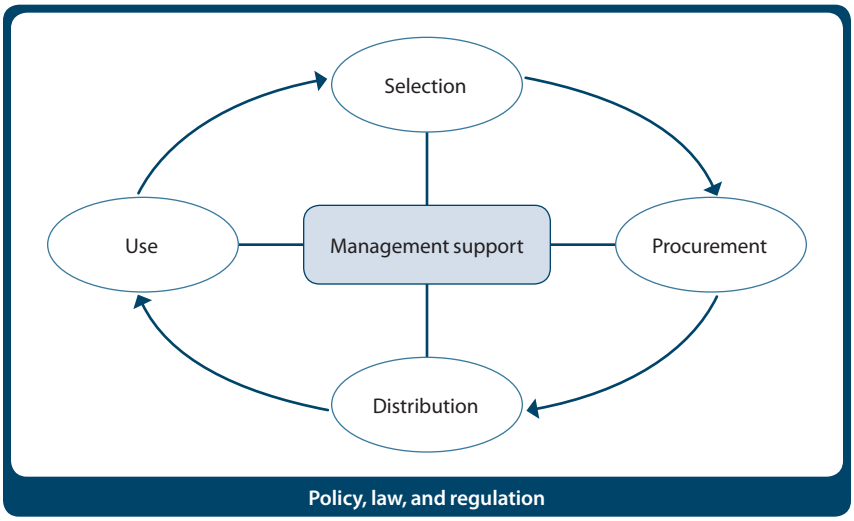
Health professionals may still think of pharmacovigilance strictly in terms of identifying and reporting previously unknown and serious ADEs related to new products; however, pharmacovigilance activities are related to every sector of the pharmaceutical management cycle. Figure 35-3 shows examples of the relationship between pharmacovigilance and pharmaceutical management.

Although many national pharmacovigilance programs are largely based on ADE reporting, a comprehensive system should encompass monitoring of medication errors and therapeutic ineffectiveness (related to poor treatment adherence, antimicrobial resistance, product quality problems, inappropriate use, or interactions); product quality problems; and communication of such information to health care professionals and consumers for risk-benefit decision making (SPS 2009). For example, as a pharmacovigilance system matures, it may expand from a program based strictly on passive ADE surveillance that relies on voluntary reports from health care providers or consumers to incorporate active surveillance methods to address priority safety concerns, such as the use of registries, sentinel sites, and follow-up of defined patient cohorts. Other system expansion efforts can include establishing a link between pharmaceutical quality assurance and ADR monitoring and developing mechanisms to communicate medicine safety information to health care professionals and the public.

A country's pharmacovigilance system should incorporate activities and resources at the facility, national, and international levels and foster collaboration among a wide range of partners and organizations that contribute to ensuring medicine safety. Figure 35-4 illustrates the components of a comprehensive, ongoing pharmacovigilance system with functions for monitoring, detecting, reporting, evaluating, and documenting medicine safety data as well as intervening and gathering information from and providing educational feedback to the reporters—prescribers, health care workers, other health care professionals, and consumers. When the information has been collected, evaluators, such as epidemiologists or pharmacologists, should analyze it to determine the adverse event's severity, probable causality, and preventability.

Significant data must be communicated effectively to a structure or entity that has the authority to take appropriate action, whether at the facility, national, or even international level. The entity may be a hospital's drug and therapeutics committee, the national pharmacovigilance center, if one exists, or the WHO Programme for International Drug Monitoring. The final function in the framework is appropriate action. If data are collected, analyzed, and reported, but no one takes any action based on the data, the system is irrelevant. The risk reduction action may be regulatory (withdrawing marketing authorization, recalling a medica-

Figure 35-3 Pharmacovigilance and the pharmaceutical management framework



Pharmacovigilance activity	Detection within the pharmaceutical management framework	Prevention
Product quality	• Most product quality issues are detected in the *distribution* portion of the pharmaceutical management cycle. • Physical inspection is done at the time of receiving the product from the supplier and at other points of *distribution* to the patient. • Complaints about efficacy occur during *use*.	• Prequalify suppliers during *procurement*. • Establish a pharmaceutical quality assurance program. • Establish a *policy and legal framework* that addresses pharmaceutical quality. • Enforce laws and regulations related to product quality.
ADRs	• *Management support* functions, such as surveillance and monitoring systems, during *use* are the primary methods for detecting ADRs.	• Consider ADR information during the *selection* process to make formulary decisions and establish standard treatment guidelines. • Report ADRs to the appropriate parties at the facility, national, and international levels. • Train health professionals about ADRs. • Communicate with patients about ADRs.
Medication errors	• Errors can be detected in all phases of the pharmaceutical management cycle: ordering, storing, labeling, compounding, dispensing, transcribing, prescribing, administering, and monitoring.	Prevention strategies should focus on all processes— • Promote a culture of safety through a nonpunitive environment for reporting events. • Improve availability of drug information. • Train and educate staff. • Consider past and potential errors when selecting products or a formulary. • Issue prescribing guidelines. • Establish dispensing and administration procedures and safeguards. • Establish monitoring guidelines. • Improve written and oral communication. • Involve patient and family in care plan.

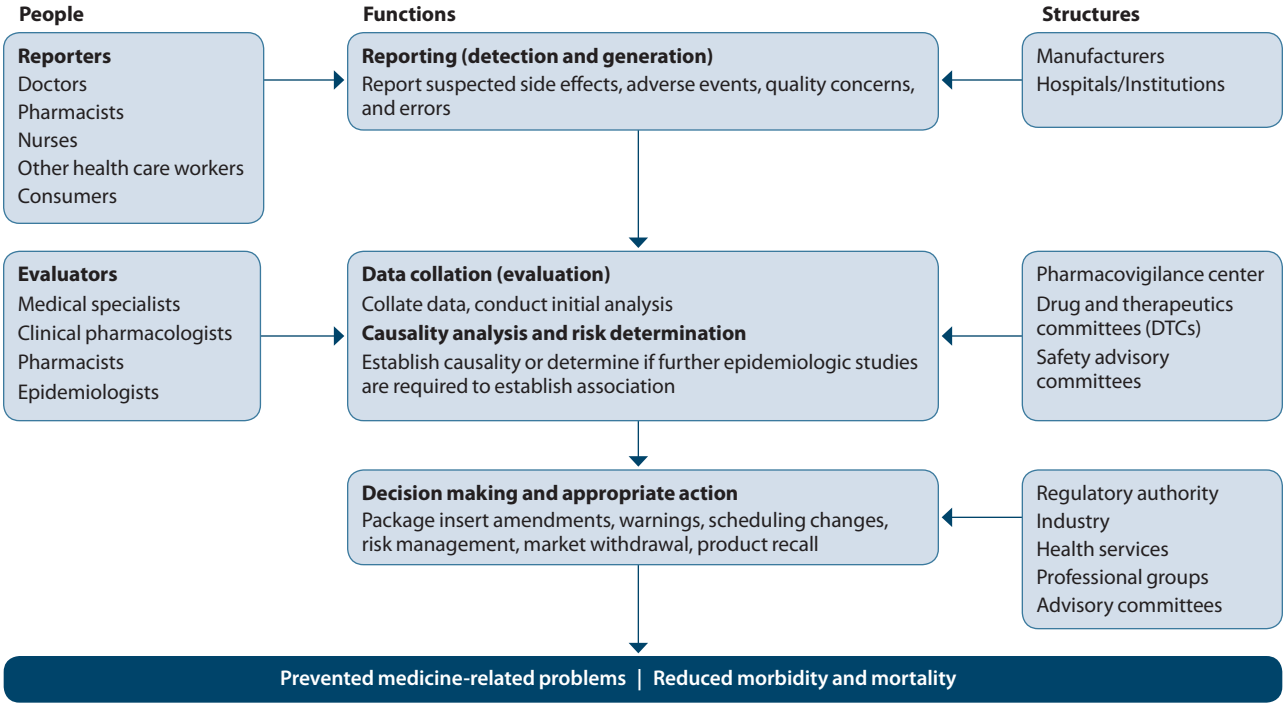
Source: CPM/MSH 2011.

tion); managerial (revising a hospital formulary, instituting distribution controls); or educational (teaching prescribers about medicine-medicine interactions or proper product handling). To encourage continued participation in the process, interventions should be shared with the data reporters as part of a feedback loop. Follow-up data collection and analysis will then measure the effectiveness of the interventions.

The outcome of a pharmacovigilance system should be decreased medicine-related problems with the ultimate effect being a reduction in morbidity and mortality.

As mentioned, pharmacovigilance activities are carried out at the facility, national, and international levels and require collaboration among a wide range of partners with differing responsibilities (Table 35-4). To plan for this information system, basic questions must be answered about

Figure 35-4 The pharmacovigilance framework



Source: CPM/MSH 2011.

whether the data flow will be separate for each area of pharmacovigilance or combined, who will be responsible for the data collection and reporting at each level of the health system, and whether vertical public health programs will be separated or integrated. For example, will the responsibility for pharmacovigilance fall under the drug and therapeutics committee (or pharmacy and therapeutics committee) at the facility level? How will pharmacovigilance drive decisions for formulary selection and treatment guidelines, changes in policies and procedures at different levels, and product approval and pharmaceutical regulation? These questions may be easier to answer if the country has a national pharmacovigilance system in place—or individual facilities developing their own systems may need to create the best information management system based on their own organization.

Pharmacovigilance activities at the facility level

Medication safety monitoring is an important part of high-quality health care in health facilities, especially hospitals. A U.S.-based study showed that ADEs in hospitalized patients resulted in significant health and economic consequences (Classen et al. 1997). Monitoring and reporting of medication errors and ADRs are important aspects of a hospital's safety system; consequently, most evidence of ADEs comes from hospitals, because the risks associated with hospital care are high and strategies for improvement are better documented. But many ADEs occur in other health care settings, such as physicians' offices, nursing homes, pharmacies, and patients' homes. However, underreporting of ADEs is a critical problem in all health care settings.

Even if a country lacks the infrastructure for coordinating national pharmacovigilance activities, hospitals usually have the capacity to design and implement a facility-based pharmacovigilance system. Effective systems for pharmacovigilance and promoting safe medication practices generally fall under the purview of the drug and therapeutics committee.

Hospital-based reports of ADRs make important contributions to clinical experience and improving the understanding of pharmacotherapy. In addition, the assessment of ADEs gives facilities the information necessary to reduce medication errors and improve health care for patients.

Pharmacovigilance activities at the national level

National governments are responsible for ensuring that medicines sold in their countries are of good quality, safe, and effective. An important component of a country's ability to monitor pharmaceutical safety is a national pharmacovigilance system that is supported by the drug regulatory authority (see Chapters 6 and 19).

Table 35-4 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 and 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

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 in 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 activities as part of public health programs

Depending on how their public health systems are organized, countries may have public health initiatives that are disease-specific and operate separately from the primary health system (for example, HIV/AIDS, tuberculosis, malaria, vaccinations), also known as vertical health programs. Such vertical programs depend on good pharmacovigilance practices (WHO/UMC 2006). Monitoring ADRs is especially important when treatment is being scaled up, such as antiretroviral therapy (ART) for HIV/AIDS, or if a change is being made in the standard treatment guidelines, such as switching to artemisinin-based combination therapies for malaria.

The major aims of pharmacovigilance in public health initiatives are the same as those of the national pharmacovigilance system. The structure and organization of the existing national systems will help determine how the public health program pharmacovigilance efforts should be designed. In some cases, the country may not have a national pharmacovigilance system. In that case, the public health program's system takes on additional importance and may provide a model for the eventual establishment of a national system. In Kenya, as ART programs scaled up and developed facility-based ADR monitoring systems, the Ministry of Health recognized the importance of national-level coordination and added pharmacovigilance to its responsibilities—a good example of a bottom-up approach to incorporating pharmacovigilance into the health care system.

WHO has a good resource on using pharmacovigilance as a tool in public health treatment programs (WHO/UMC 2006).

Pharmacovigilance activities at the international level

The patterns of how people access and use pharmaceuticals are changing because of globalization, free trade, and increased use of the Internet (WHO 2004). These changing patterns require that pharmacovigilance activities around the world become more closely linked and therefore better able to respond to how medicines are being used in society.

At the international level, WHO initiated its Programme for International Drug Monitoring in 1968 to pool existing data on ADRs from ten countries. With its Uppsala Monitoring Centre, the WHO program now works with national pharmacovigilance programs in almost 100 countries (UMC 2010). The Uppsala Centre maintains the database of ADR reports—one of the largest in the world with more than 5 million case reports. The Uppsala Centre established standardized reporting by all national centers and facilitates communication between countries on medicine safety issues.

The Institute for Safe Medication Practices (http://www.ismp.org) has established a forum for individual health care providers and consumers in any country to confidentially share information on ADEs. Although the system was established for U.S.-based reporting, the institute welcomes reports from anywhere in the world. Health care professionals and consumers can submit reports and associated materials in confidence. After removing the identifiers, the information is shared with the U.S. Food and Drug Administration, the manufacturer, and others to inform them about pharmaceutical labeling, packaging, and nomenclature issues that may promote errors by their design.

Major components of a pharmacovigilance system are data collection, which can be voluntary or nonvoluntary, and data analysis and reporting.

35.3 Data collection

Passive data collection

Passive reporting of ADRs and medication errors (also known as voluntary case reporting) requires health care providers to be active participants in a culture of safety. Programs relying solely on voluntary, spontaneous reporting methods reveal only the tip of the iceberg, and calculated medication event rates are more an indication of reporting rates than actual occurrence rates. However, voluntary reporting should always be encouraged, because it helps establish a team approach to improving patient care and reducing risks.

Barriers to voluntary reporting of medication events are—

- Fear of punishment by supervisors or fellow workers (in the case of an error)
- Fear of liability for the provider or facility
- Failure to recognize that an incident has occurred
- Unclear or cumbersome methods for reporting
- Poor track record of improvements by the institution
- Lack of time

The objective of a successful monitoring system is to learn from and correct sources of error rather than to punish offenders. In addition to driving out fear, facilities should try to improve error tracking through education programs that promote voluntary reporting and by communication to staff about the improvements resulting from medication events reported.

Mandatory data collection

Many country regulations require manufacturers and distributors of pharmaceuticals to report information on ADRs that they gather during postmarketing surveillance to health authorities. In addition, facilities seeking accreditation may be required to have an ADE collection system in place as part of the process to receive official recognition. Some countries require health care professionals to report ADEs, but the effectiveness of such legislation is unknown (WHO/UMC 2000).

Active data collection

Active data collection of medication events is carried out as a focused and structured activity and includes trigger tools, patient chart audits, and direct observation methods. Using a consistent methodology for active data collection provides more reliable calculated medication event occurrence rates and evidence of trends.

Trigger tools provide clues that an ADR occurred. Triggers are identified from either computerized reports or manual review methods to identify alerting orders, laboratory values, or clinical conditions. Further research into these triggers may help identify ADRs that have occurred or that are currently evolving—

Laboratory triggers are identified from defined parameters indicating an ADR might be associated (serum glucose under 50, white blood cell count below 3,000, platelets below 50,000, toxic drug levels, and the like).

Medication order triggers are prescription orders for antidotes or reversal agents such as dextrose 50 percent 50-mL injection, glucose tablets, diphenhydramine,

steroids, naloxone, epinephrine, or sudden change or stoppage of a patient's medication ("discontinue digoxin, quinidine, potassium chloride").

Clinical triggers are patient conditions often associated with ADRs, such as rash, falls, lethargy, or apnea.

Trigger detection methods yield more data than voluntary reports (Jha et al. 1998), and more sophisticated methods combine composite triggers (such as laboratory tests and medication orders) for better yields (Schiff et al. 2003).

Whereas trigger tools can help identify the patients and medications most likely implicated in an event, *chart review* is used to identify potential ADRs, medicine interactions, and medication errors. These reviews can be conducted prospectively, concurrently, or retrospectively. Retrospective reviews are often more convenient for data collection, although the time lapse since the event makes in-depth investigation difficult. Medical records classified by codes, such as ICD-10 (International Classification of Diseases, Tenth Revision) codes that indicate an ADR, provide a method to identify suspicious charts.

A prospective study might focus on recording any possible adverse event in every patient receiving a new medicine. For instance, the Ghana National Centre for Pharmacovigilance developed a simple form for facilities to document and report ADRs in pregnant women associated with a change in recommended treatment from chloroquine to sulfadoxine-pyrimethamine to prevent malaria (Dodoo 2005). Combined with their demographic information, the information collected on this cohort of patients can provide an effective way of identifying previously unrecognized ADRs (WHO/UMC 2000). Prospective and concurrent reviews can also detect potential adverse events before they happen or as they are evolving, so that patient harm can be avoided or minimized.

Direct observation provides an abundance of useful data on medication errors and helps to identify weaknesses in the medication-use process. Observers can be placed at any point in the medication-use process, but medication administration is often one of the most problematic areas and easiest to observe. If the data collection method is consistent, the resulting error rates are reliable and allow improvements to be measured. 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 35-5 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.

A study comparing three methods for detecting errors—direct observation, chart review, or voluntary adverse event reporting—showed that direct observation was far more efficient and accurate in detecting medication errors (Flynn et al. 2002). Direct observation can also be used as a training and orientation tool for new employees by ensuring that new employees have a minimal level of competency and understand the facility's medication administration process.

Data collection tools

ADR and medication error data are usually collected by filling out a standardized form, thereby providing convenience and consistency. Data collection tools should be adapted from standards of practice and procedures, and the data fields on the form determined by how the data are eventually summarized and used. Ideally, if a country has a national pharmacovigilance program, the reporting form is standardized for use in all settings throughout the country.

For ADR data, identifying specifics about the patient is important. These include concomitant therapies and conditions, the patient's reaction to the medicine, and the medicine suspected of causing the reaction together with the manufacturer and batch number, if available. WHO gives guidance on what to include on a data collection form (WHO 2002) (see also Box 6-2 on adverse drug reaction monitoring in Chapter 6).

For medication error data, collecting information that can be analyzed for improvements to the medication-use system is important. Systems may have separate forms for tracking product quality problems, ADRs, and medication errors, or systems may use one form and process. Figure 35-6 shows a sample ADE reporting form that also combines reporting for product quality problems in Zambia.

35.4 Data analysis and reporting

After the ADR data have been collected, they should be analyzed to determine severity, probable causality, and preventability. Specific algorithms and classification systems have been developed for these analyses—

Severity (impact on the patient's health): Table 35-5 shows a classification for determining the severity of ADRs. It addresses both ADEs associated with medication error

Figure 35-5 Nonvoluntary data collection tool for pharmacovigilance

Medication Administration Audit Tool

Date: Unit: Name of Evaluator:

Checklist for medication administration	Patient #1		Patient #2		Comments
	Met	Not met	Met	Not met	
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).					

Source: Feinberg 2001.

MAR = medication administration record.

Figure 35-6 Sample ADE/product quality problem form from Zambia

Zambia Pharmacovigilance Centre (ZPVC) in Lusaka
ADR Case Report Form
For adverse drug event and product quality problem reporting

In collaboration with the WHO International Drug Monitoring Programme

All information provided here will be treated as strictly confidential.

CLIENT INFORMATION

Name (or initials):			Age:	Weight (kg):
Sex: M F	LMNP / / (if female)	DOB: / /		Height (cm):

ADVERSE EVENT/PRODUCT QUALITY PROBLEM

Adverse event (Form Part 1)	And/or product quality problem (Form Part 2)	Date of onset of reaction: / / Time of onset of reaction: _____ h _____ min

Description of reaction or problem (Include relevant tests/lab data, including dates):

1. MEDICINES/VACCINES/DEVICES (Include all medicines taken concomitantly.)

Trade Name and Batch No. (Asterisk Suspected Product)	Daily Dosage	Route	Date Started	Date Stopped	Reasons for Use

ADVERSE REACTION OUTCOME (Check all that apply.)

☐ Death	☐ Life-threatening event	Event reappeared on rechallenge:	Recovered: Y N
☐ Disability	☐ Hospitalization	Y N Rechallenge not done	Sequelae: Y N
☐ Congenital anomaly	☐ Other:	Treatment (of reaction):	Describe sequelae:
☐ Required intervention to prevent permanent impairment/damage			

COMMENTS: (e.g., relevant history, allergies, previous exposure, baseline test results, laboratory data)

2. PRODUCT QUALITY PROBLEM

Trade Name	Batch No.	Dosage Form and Strength	Expiry Date	Size/Type of Container

Product available for evaluation? Y N

REPORTING DOCTOR/PHARMACIST:

Name Telephone no.	Address

Qualifications

Signature	Date

This report does not constitute an admission that medical personnel or the product caused or contributed to the event.

Source: Zambia Pharmacovigilance Centre, Lusaka, Zambia.
DOB = date of birth; LMNP = last menstrual period.

Table 35-5 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.

and those not associated with error, so it can be applied to all medication events.

Probable causality (likelihood that the medicine's use or lack of use contributed to the ADR): Table 35-2 illustrates how to calculate the Naranjo Probability Score, a common method for determining whether a particular medicine was actually related to the ADR.

Preventability (Was an error associated with the event?): Box 35-2 is an algorithm used to help determine if the ADE was caused by a medication prescribing error, and therefore, preventable.

For ADEs that are considered preventable, identifying where the primary error occurred and what aspects contributed to the system breakdown is useful; therefore, analysis and reporting should facilitate this activity by identifying and targeting problem-prone areas, such as specific steps in the process (prescribing practices), medication types (injectables), disease states or patient types, employees (new employees, interns), patient care areas (surgery), and time of the day (night shift). For example, if data indicate that ADEs are caused by nurses giving the wrong dose of injectable medications, then focused activities for improvement should be developed. These activities might include educational activities and procedural changes, such as independent double-checks of all injectable medications. After implementing the interventions, the error rate can be checked for improvement.

Medication event data are organized on manual or electronic spreadsheets, which help summarize and sort data for reporting at the facility or regional level. National and international programs often use Internet-based ADR or medication error databases to collect and share data. (See References and Further Readings.)

ADRs should be reported to the national ADR program, if one exists, as well as to the pharmaceutical manufacturer; the latter is especially important if the ADR has not been reported previously in the literature or is not included on the product's label. Reporting the results of ADR and medical error analysis to the organizational body within a hospital or facility that has responsibility for medicine safety, such as the drug and therapeutics committee, is also important.

Box 35-2
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 monitoring 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.

Country Study 35-1 shows how a research hospital in India established an ADR reporting system.

35.5 Taking actions for improvement

When ADEs occur, they must be analyzed and reported, and their significance should be communicated effectively to an audience that has the knowledge to interpret the information. National or even international actions that can result from the appropriate reporting of ADEs include—

- Pharmaceutical manufacturers sending out "Dear Doctor" letters to alert health care providers of newly discovered adverse reactions
- Pharmaceutical manufacturers revising medicine package inserts that reflect the new information
- Pharmaceutical manufacturers or national regulatory authorities instigating a medicine recall

At the clinical level, actions concerning serious or recurring ADEs include—

- Changing the medication formulary if necessary
- Implementing new prescribing procedures
- Implementing new dispensing procedures
- Modifying patient-monitoring procedures
- Educating professional staff (face-to-face; in-service education; bulletins; reports of collected ADRs)
- Educating patients

Most important at the clinical level, however, is taking action to improve medication safety and decrease medication events by developing a culture of safety in the health care organization (see Box 35-3). For example, the organization's leadership should maintain a clear commitment to safety by emphasizing that safety takes priority over production or efficiency; employee job descriptions and performance evaluations should include a component for participation in safety initiatives that are supported by recourses, rewards, and incentives; and the response to a problem should focus on improving system performance.

Country Study 35-2 illustrates the standard operating procedures and possible actions for addressing recurring ADRs in an ART program in Kenya. In a report on preventing medication errors, the Institute of Medicine (IOM 2006) urged that doctors, nurses, pharmacists, and other health care providers communicate more with patients about the risks, contraindications, and possible adverse reactions from medications and what to do if they experience an ADE. In addition, patients should be encouraged to take a more active role in their own medical care and should be given plenty of time to consult with health care providers about their medications (see also WHO's patient safety initiative, http://www.who.int/patientsafety/en).

In summary, the use of medicines involves a trade-off between benefits and potential for harm. Pharmacovigilance can help minimize the harm by ensuring that medicines of good quality are used rationally and that the expectations and concerns of the patient are taken into account when

Country Study 35-1
Implementing an ADR reporting system in India

ADR monitoring and reporting systems are uncommon at the local level in developing countries. Although India has a national ADR monitoring center in New Delhi, Kasturba Hospital, a 1,400-bed, tertiary care teaching hospital in Manipal had never had an ADR program before 2001. It established an ADR monitoring center not only to improve medication safety practices in the district, but also to provide a link between the region and the national center. The Kasturba Hospital program was launched and is maintained by the pharmacy department using established ADR-reporting centers in India as models.

The Kasturba Hospital system relies on physicians and pharmacists working together. When a physician detects an ADR, he or she fills out the reporting form and sends it to the pharmacy department, where a pharmacist follows up on the ward with an investigation of the incident. Pharmacists may also report ADRs on their own. When the documentation is complete, the pharmacist analyzes the causality, preventability, and severity of the ADRs using various scales, then issues the results quarterly. Physicians who report ADRs may be given information on how to manage the reaction, and if it involves an allergy, the pharmacist counsels the patient and provides an alert card for the patient to give his or her health care provider. In the first year of the program, 142 ADRs were reported, including several rarely seen reactions, among them cisplatin-induced hiccups. As a result of the new program, the Kasturba Hospital staff saw an increase in the awareness of the importance of ADR monitoring and reporting and improved interactions between the physicians and the pharmacists.

Source: Mohan, Rao, and Rao 2003.

Box 35-3
Safe medication practices

- Encourage staff to report ADRs, errors, and unsafe conditions.
- Change the safety culture from punitive to participatory.
- Standardize abbreviations, and develop a list of dangerous abbreviations, acronyms, and symbols to avoid.
- Write or print clearly.
- Review medication orders for appropriateness before dispensing and administration.
- Clarify medication orders that are not clear or do not make sense for the patient's clinical condition.
- Provide health care providers with access to drug information.
- Read back and receive confirmation on all verbal and telephone orders.
- Identify look-alike and sound-alike products and take action to avoid mix-ups (for example, physically separate storage, clearly differentiate appearance, purchase alternatives, use generic versus brand name or vice versa to differentiate from sound-alike product).
- Label all medications in a standardized manner according to hospital policy.
- Dispense medications labeled for a specific patient and in the most ready-to-administer dosage form.
- Follow the five "rights" of drug administration: right patient, right drug, right time, right dose, and right route.
- Verify patient identification against labels and orders prior to medication administration.
- Develop a list of problem-prone or high-risk medications and implement strategies to minimize the risk.
- Standardize or limit the number of drug concentrations available in the organization.
- Remove high-risk medications from patient care areas (for example, concentrated electrolytes).
- Involve patients in their care: tell them the name of the medicine and its purpose before administration.

health care providers are making decisions about therapy. WHO (2004) lists the best ways to achieve these goals—

- Serving public health and fostering a sense of trust among patients in the medicines they use that also extends to confidence in the health service in general
- Ensuring that risks in medicine use are anticipated and managed
- Providing regulators with the necessary information to amend the recommendations on the use of medicines
- Improving communication between the health professionals and the public
- Educating health professionals to understand the effectiveness and risk of medicines that they prescribe. ■

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★ = Key readings.

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Country Study 35-2
Standard operating procedures for aggregating ADR data and taking appropriate action in an ART program in Kenya

The Coast Provincial General Hospital in Mombasa, Kenya, was one of the first public facilities in the country to offer ART to AIDS patients. Hospital administrators and program managers realized the importance of monitoring and reviewing ADRs related to the use of these new, powerful antiretroviral medicines to ensure optimal treatment outcomes and patient safety. The ART program staff designed and implemented standard operating procedures for ADR monitoring for all staff involved with the ART program.

All ART patients' ADRs are reported on an ADR form. The forms are reviewed, compiled, examined for trends, and reported, and appropriate actions are taken in response to the ADR report. Actions can be taken at the individual patient level or, in the case of a noted trend, at the system level. A summary of the procedures for aggregating the individual ADR data follows.

Pharmacist in charge of the ART program—

1. Reviews the *ART ADR Forms* and *ART ADR Reports* and prepares the *ADR Summary Report* at the end of each month
2. Looks for unusual trends
3. Reviews the *Actions Taken* section of the reports submitted to ensure that appropriate actions have been taken as decided by the ART Eligibility Committee based on the outline in the following table
4. Presents the *ADR Summary Report* to the ART Eligibility Committee at the first meeting of each month
5. Reports on unusual trends
6. Reports on inappropriate actions taken

The ART Eligibility Committee—

1. Reviews the *ADR Summary Report* and, if necessary, the raw data
2. Decides to take appropriate actions in response to *ADR Summary Reports* or unusual trends or inappropriate actions taken (possible actions are outlined in the following table)
3. Forwards the *ADR Summary Reports* and presents the findings to the Scientific Committee

The Scientific Committee reviews the *ADR Summary Report* and decides on appropriate action to be taken.

Suggested trends and actions for the data fields appearing on the *ADR Summary Report* and the *ART ADR Form* appear in the following table. This table is not all inclusive; it merely provides a starting point for the ART Eligibility Committee, Scientific Committee, and Steering Committee to use when evaluating the *ART ADR Reports*.

ADR actions on an aggregate level

Trends	Possible actions
An increase in suspected or probable ADRs associated with a specific age group, gender, pregnancy status, drug class, or particular medicine	• Notify the Scientific Committee. • Medicine may be used cautiously in particular groups with extra patient monitoring (lab or clinic visits) required. • Medicine may not be given to particular groups. • Medicine may be removed from treatment plan. • ADR may be reported to the Pharmacy and Poisons Board by the Steering Committee on the recommendation of the Scientific Committee. Pharmacy and Poisons Board may inform the manufacturer. • ART Eligibility Committee or Scientific Committee will investigate possible causes of this increase and take appropriate corrective or preventive actions.
Serious ADRs associated with ADR probability category definite or probable • not listed in the product labeling or • occurring in medicines less than five years since first approved by the Pharmacy and Poisons Board	• Notify the Scientific Committee. • Medicine may be used cautiously with extra patient monitoring (lab or clinic visits) required. • Medicine may be removed from treatment plan. • ADR may be reported to the Pharmacy and Poisons Board by the Steering Committee on the recommendation of the Scientific Committee. Pharmacy and Poisons Board may inform the manufacturer.
Appropriate actions not being taken in response to suspected ADRs as decided by the ART Eligibility Committee	• Organize a training session. • Discuss with individual prescribers.

Source: Standard Operating Procedures for ART Pharmacy, Coast Provincial General Hospital, Mombasa, Kenya.

ASSESSMENT GUIDE

National activities

- Does the country address pharmacovigilance as part of its pharmaceutical legislation?
- Do any national policies and practices exist that are related to pharmacovigilance?
- Who is responsible for overseeing national pharmacovigilance activities?
- Does a national pharmacovigilance center exist? If so, where is it housed?
- Does the national pharmacovigilance program have a relationship with WHO's Programme for International Drug Monitoring?
- Does a national ADR monitoring and reporting system exist? If so, how many reports were submitted during the previous year? What is done with the reports?
- Is a system in place to report product quality problems? In the previous year, how many reports were submitted on medicine product problems?
- Are reports of medical errors collected and analyzed at the national level?
- Are the three areas—ADRs, product quality problems, and medication errors—combined in one reporting stream or separate streams?
- How is important information about ADRs communicated to health professionals? To the industry? To the media? To consumers?
- Is pharmacovigilance included in university curricula for health care professionals?

Public health program activities

- Do the country's public health programs (for example, HIV/AIDS, tuberculosis, malaria) have their own ADR reporting systems? If so, what is the reporting structure?
- Do the public health programs integrate their pharmacovigilance activities with national-level activities?

Facility activities

- Does the facility track information on ADRs in patients? Request an example of a recent report. Is reporting passive (voluntary) or active (nonvoluntary)?
- Does the facility track medication errors?
- What committee oversees the pharmacovigilance activities, and when did it last review a pharmacovigilance report?
- Does the facility have a culture of safety, that is, do employees feel comfortable reporting information on medication errors and ADRs? How many voluntary reports did the facility have in the last year?
- To whom are ADRs and medication errors reported? What is the mechanism?
- Does the organization have an internal mechanism to analyze and address problems with medication safety? Give examples of recent actions.

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