

Supporting Pharmacovigilance in Developing Countries

The Systems Perspective



About SPS

The Strengthening Pharmaceutical Systems (SPS) Program strives to build capacity within developing countries to effectively manage all aspects of pharmaceutical systems and services. SPS focuses on improving governance in the pharmaceutical sector, strengthening pharmaceutical management systems and financing mechanisms, containing antimicrobial resistance, and enhancing access to and appropriate use of medicines.

Recommended Citation

This report may be reproduced if credit is given to SPS. Please use the following citation.

Strengthening Pharmaceutical Systems (SPS). *Supporting Pharmacovigilance in Developing Countries: The Systems Perspective*. Submitted to the U.S. Agency for International Development by the SPS Program. Arlington, VA: Management Sciences for Health.

Introduction

THE DEVASTATION caused by the HIV/AIDS pandemic helped draw attention to the lack of access to medicines in resource-constrained areas—especially sub-Saharan Africa. In response, new funding sources, such as the President’s Emergency Plan for AIDS Relief, the President’s Malaria Initiative, and the Global Fund to Fight AIDS, Tuberculosis and Malaria, have made unprecedented sums of money available to procure essential medicines, including new products such as antiretroviral (ARV) medicines for HIV/AIDS, artemisinin-based combination therapies (ACTs) for malaria, and second-line medicines for multidrug-resistant tuberculosis. The Global Fund alone has approved grants for over 15.5 billion U.S. dollars (USD), with almost half allocated for medicines and commodities (Global Fund 2009).

With increased access to essential medicines comes a greater need to monitor and promote the safety and effectiveness of these medicines. Few developing countries, however, have the structures, systems, or resources in place to support medicine safety activities, and countries often lack unbiased, evidence-based information to help guide treatment decisions and promote rational—that is, safe, effective, and cost-effective—use of medicines. In addition, sustained budgetary support for pharmacovigilance and medicine safety activities is generally lacking.

The Strengthening Pharmaceutical Systems (SPS) Program has developed a conceptual framework and operational approach to strengthen pharmacovigilance systems. Although designed to be applied in resource-constrained settings, this framework and approach will be useful to all involved in promoting access to and rational use of essential medicines, such as U.S. Agency for International Development (USAID) staff, ministries of health in developing countries, international donors, health care workers, health policy makers, and other stakeholders who recognize the need for strong pharmacovigilance systems.

This report is made possible by the generous support of the American people through the U.S. Agency for International Development (USAID), under the terms of cooperative agreement number GHNA-00-07-00002-00. The contents are the responsibility of Management Sciences for Health and do not necessarily reflect the views of USAID or the United States Government.

Impact of Medicine Safety

Many studies have reported the huge impact that poor product quality, adverse drug reactions (ADRs), and medication errors have on health care in general and on patients' health in particular, but because most cases go undetected, estimating the actual scale of this burden is almost impossible. Much of the documented evidence available on medicine quality and ADRs comes from industrialized countries; for example, in its seminal report of 1999, the U.S. Institute of Medicine estimated that up to 98,000 people die each year from medication errors in U.S. hospitals at a cost of up to USD 29 billion per year (Kohn et al. 1999). Authors of a meta-analysis estimated that ADRs alone—excluding medication errors—killed over 100,000 people in 1994 and were the fourth to sixth leading cause of death in the United States (Lazarou et al. 1998). A similar study estimated that over 70 percent of ADRs that resulted in hospitalization in the United Kingdom could have been avoided (Pirmohamed et al. 2007). Adverse drug events (ADEs) also are costly in terms of patients' loss of trust in the health care system.

The costs in lives and money is great in high-income countries, but the situation in low- and middle-income countries is likely to be much worse because of the poorer state of health system infrastructure, unreliable supply and quality of medicines, and lack of adequately trained health care staff. Many developing countries are now recognizing the need to set up systems to monitor the safety of newly introduced medicines, such as ACTs and ARVs, but they often lack the resources, including in-country expertise, to design and build a pharmacovigilance system from the ground up. Proper attention to pharmacovigilance as an integral component of rational pharmaceutical management has the potential, however, to greatly reduce such preventable adverse events and contribute valuable evidence on which to base benefit-risk assessments.

What Is Pharmacovigilance?

Simply put, pharmacovigilance is a system to monitor the safety and effectiveness of medicines and other pharmaceutical products. The World Health Organization (WHO) defines pharmacovigilance as “science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other possible drug-related problems” (WHO 2002). A pharmacovigilance system should include all entities and resources that protect the public from medicine-related harm, whether in personal health care or public health services. The pharmacovigilance system aims to achieve this protection through efficient and timely identification, collection, and assessment of ADEs, and by communicating risks and benefits to support decision making about medicines at various levels of the health care system.

When people take medicines, they may suffer adverse clinical events, such as dizziness, headache, skin rashes, or other symptoms, but not all adverse events

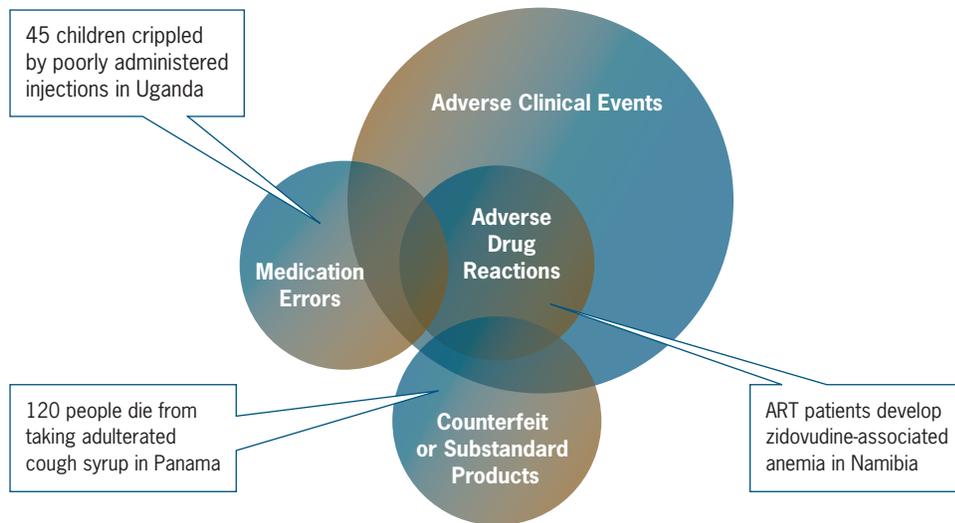


FIGURE 1.
Medicine-related
sources of adverse
clinical events

Adapted from Barker et al. 2002; Ferner and Aronson 2006; Nebeker et al. 2004

are caused by medicines; some may result from the patient’s illness or condition, genetic or environmental factors, diet, or other causes. ADEs are directly related to medicines and may be due to poor product quality, medication error (in prescribing, preparing, administering, or taking the medicine), or known or unknown pharmacological properties (resulting in ADRs) (figure 1). Non-ADR adverse events resulting from medication errors and product quality problems include lack of therapeutic effect and antimicrobial resistance.

ADEs are preventable when they are the result of a medication error, or they can be unpreventable, for example, if a patient had an unknown medication allergy. Documenting 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, and treatment guidelines, or even in a product recall. Medication errors and poor-quality products may not always cause ADEs, but they should not be ignored. Identifying and documenting potential ADEs is useful because they can identify problem areas that might be corrected before harm occurs, such as a communication problem within the health facility or two easily confused labels.

Therefore, pharmacovigilance programs should monitor events that may be related to **product quality, medication errors, and previously known or unknown ADRs.**

Product Quality

Monitoring the quality of products available in the marketplace should identify products that are defective, deteriorated, or adulterated because of poor manufacturing practices, inadequate distribution and storage, or tampering. Medicines that have lost their potency after being stored at high temperatures would fall under this category, for example, as would counterfeit products. Many studies have documented the circulation of counterfeit and substandard medicines,

especially antimalarials, in developing countries (e.g., Atemnkeng et al. 2007; Bate et al. 2008; Onwujekwe et al. 2009).

An example of the impact of medicine quality occurred in the mid-1990s, when almost 100 children in Haiti died from ingesting locally manufactured pain relief syrup adulterated with diethylene glycol. In a published report of the incident, O'Brien and colleagues (1998) said, "This outbreak highlights the challenges in developing countries where there may not be adequate regulation, enforcement, or strict implementation of current good manufacturing practice regulations in the pharmaceutical sector." They went on to conclude that "It is likely that disasters such as these will continue to occur until ... countries around the world adopt and enforce regulations that ensure the safety of pharmaceutical products." Unfortunately, those words proved prescient when a remarkably similar incident involving diethylene glycol in locally manufactured cough syrup killed over 120 people in Panama about 10 years later. A lengthy investigation identified a number of contributing factors, including problems with adulterated raw ingredients, labeling, poor controls along the supply chain, and a lack of testing by the laboratory where the syrup was manufactured (Rentz et al. 2008). The government had given the laboratory, which did not follow good manufacturing practices, a permit to operate and did not require registration of the laboratory's products, which would have entailed quality control tests.

Medication Errors

The National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) 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" (NCC MERP 2009). Errors can be harmless or detrimental to the patient. A study of 36 health care facilities in the United States showed that nearly one in five doses of medication were given in error and 7 percent had the potential to cause patient harm (Barker et al. 2002), and the U.S. Institute of Medicine in 2006 estimated that more than 1.5 million Americans are injured every year by preventable medication errors (Aspden et al. 2006).

Medication errors result from faulty systems, processes, and conditions that lead people to make mistakes or fail to prevent mistakes. Problems can result from illegible handwriting, use of dangerous abbreviations, overlooked interactions with other medicines, oral miscommunications, and sound-alike or look-alike products. For example, a recent number of highly publicized injuries and deaths have involved infants receiving overdoses of heparin because of confusing labels, mixture miscalculations, or faulty verification by a health care provider (ISMP 2008); in Uganda, over 45 children were crippled from nerve damage caused by improperly injected quinine (Agiro 2009). By definition, medication errors should be preventable through education and effective systems controls involving pharmacists, prescribers, nurses, administrators, regulators, and patients.

Adverse Drug Reactions

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

An ADE is caused by either the medicine itself *or* the medicine's inappropriate use. Therefore, an ADR is always an ADE, but the ADE category also includes results from, say, an overdose because of a dispensing error or some other error occurring when the patient is taking the medicine (figure 1).

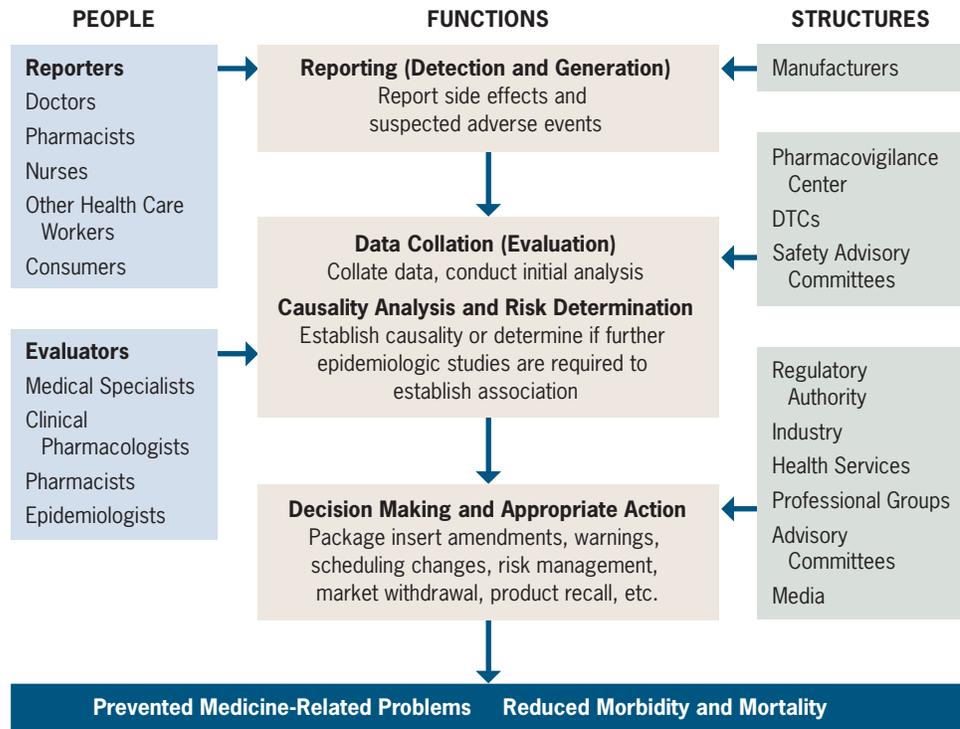
When a new medicine is being developed, it goes through several phases of testing for safety and efficacy, first with animals, then with human volunteers. When a product is approved, however, it may have been tested in only a limited number of patients—orders of magnitude less than are likely to use the product once it is approved. Therefore, premarketing studies generate incomplete information on safety relative to the full profile of likely users, including sensitive groups whom clinical trials do not include, such as children, pregnant women, and the elderly. As a result, postmarketing surveillance is a critical tool for completing the safety and effectiveness profile of a new medicine.

Pharmacovigilance: A Comprehensive System Perspective

Health professionals may still think of pharmacovigilance strictly in terms of identifying and reporting previously unknown and serious ADRs related to new products. Although many national pharmacovigilance programs are largely based on this activity, a comprehensive system should also 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. For example, as a pharmacovigilance system matures, it may expand from a program based strictly on passive ADR 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.

FIGURE 2.

The pharmacovigilance framework: relating people, functions, structures, and expected outcome and impact



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 2 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. Once 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. A number of resources are used for such analysis, such as the Naranjo algorithm for causality analysis (Naranjo et al. 1981). 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 (DTC), the national pharmacovigilance center, if one exists, or the WHO Program for International Drug Monitoring. The final function in the framework is **appropriate action**. If data are collected, analyzed, 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 medication); 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 impact being a reduction in morbidity and mortality.

As countries move to expand the scope of their pharmacovigilance activities to include monitoring for product quality problems and adverse events related to inappropriate medicine use, they will need to establish new mechanisms for cooperation among stakeholders and build system capacity. For example, incorporating product quality surveillance into the system used for ADR reporting may require linkages between the entity responsible for collecting, compiling, and evaluating ADR reports and the national pharmaceutical inspectorate and quality control laboratory.

Data collection and reporting on the three potential sources of ADEs—product quality problems, medication errors, and ADRs—must be incorporated into the overall health system, from the facility to the national level. To plan for this information system, basic questions must be answered about whether the data flow will be combined for each of these potential sources, who will be responsible for the data collection and reporting at each level of the health system, and how vertical public health program reporting will be integrated. For example, is a functioning DTC in place to take responsibility for pharmacovigilance at the facility level? How will pharmacovigilance data drive decisions for formulary selection and treatment guidelines, changes in policies and procedures at different levels, and product approval and pharmaceutical regulation?

SPS works with countries to answer such questions and to map out a phased plan to implement a comprehensive system that includes activities at the facility, national, and international levels and establishes links between stakeholders.

Pharmacovigilance Methods

Spontaneous or passive adverse event reporting by health care providers and patients is useful in identifying unexpected and rare adverse events. Although the strengths and limitations of spontaneous reporting approaches have been described elsewhere, it is important to note that this approach is the one most frequently used to detect medicine safety problems, but that it often needs strengthening in resource-constrained settings.

Active surveillance involves methodically searching for exposures or events at sentinel site facilities, in addition to following up patients who have been exposed to medicines of interest. This systematic approach is designed to collect more comprehensive ADE data than passive surveillance and is, not surprisingly, more expensive than spontaneous reporting. Active surveillance methods allow analysts to obtain a denominator of persons exposed to medications of interest, which

allows for the calculation of ADE rates and which can highlight medication safety among vulnerable populations, such as women of childbearing age and children. An example of active surveillance is cohort event monitoring, which entails following up patients treated with a particular medicine and collecting information on outcomes. Although versions of cohort event monitoring were developed more than 20 years ago, this methodology has received renewed interest.

A registry, which follows up patients presenting with the same characteristic(s), falls under the category of active surveillance. This characteristic can be a disease (disease registry) or a specific exposure (drug registry) or a type of exposure occurring during a specific life event (pregnancy exposure registry). Registries include information gathered prospectively using standardized questionnaires. The most commonly used method to systematically assess post-approval drug safety in pregnancy is the use of a pregnancy exposure registry. Others have also advocated for using registries to assess the safety of antimalarial medicines (Dellicour et al. 2007; Ward et al. 2007; WHO and MMV 2009).

Formal observational studies identify and quantify the strength of associations between a given medication exposure and adverse health outcome. These types of studies include case-control and cohort studies. Pharmaceutical manufacturers sometimes conduct clinical trials during the postapproval stage when preapproval clinical trials identify significant risks. In some instances, researchers might also conduct pharmacodynamic and pharmacokinetic studies to determine whether particular dosing regimens put patients at an increased risk of adverse events.

Pharmacovigilance at the Facility Level

Even though medication safety monitoring is an important part of quality health care, ADEs occur in other health-care settings, such as clinics, nursing homes, pharmacies, and patients' homes. Under-reporting of ADEs is a critical problem in all settings. Hospital-based reports of ADRs make important contributions to clinical experience and toward an understanding of pharmacotherapy. In

BOX 1. STRENGTHENING THE CAPACITY OF DRUG AND THERAPEUTICS COMMITTEES TO PROMOTE MEDICINE SAFETY

In 21 DTC courses (including a session on managing ADRs), Rational Pharmaceutical Management (RPM) Plus/SPS and partners have trained more than 800 participants from 69 countries, who established or restructured more than 85 DTCs and implemented hundreds of DTC-related interventions in resource-constrained settings. In Namibia, SPS developed a strategy to strengthen five regional therapeutics committees to serve as models for other regions in the country. SPS also conducted several sensitization and training seminars for pharmacists, specialists,

and medical directors in Ethiopia about how DTCs can contribute to hospital operations, resulting in 80 newly functioning DTCs. Similarly, Rwanda has trained 165 health professionals in how to establish and operate DTCs. SPS gives the hospitals ongoing support to help institutionalize the committees. In one hospital in Kenya, monitoring of adverse drug-related events led the DTC to develop and implement guidelines for prescribing and preparing vancomycin and to remove cough and cold remedies from the hospital formulary.

addition, the assessment of ADEs gives facilities the information needed to reduce medication errors and improve health care.

A well-established network of DTCs can play a valuable role in implementing pharmacovigilance activities in the health facility or area under its jurisdiction, for example, by taking measures to address irrational use and prevent medication errors at the local level. SPS has worked extensively with DTCs to build capacity in medicine safety and rational use (box 1).

Pharmacovigilance at the National Level

National governments are responsible for assuring that medicines sold in their countries are of good quality and are safe and effective. An important component of a country's ability to monitor medicine safety is a national pharmacovigilance system that is supported by the medicine regulatory authority. A national pharmacovigilance program can be housed in a national pharmacovigilance center or in a tertiary or research-oriented hospital. In the traditional model, a pharmacovigilance system is centralized and consists of one national center

BOX 2. BUILDING CAPACITY IN MEDICINE SAFETY— NAMIBIA'S THERAPEUTICS INFORMATION AND PHARMACOVIGILANCE CENTER

A 2003 assessment in Namibia identified the lack of both a national medicines information center and an ADR monitoring system as critical gaps in Namibia's delivery of antiretroviral therapy (ART). In collaboration with the Ministry of Health and Social Services (MoHSS), SPS integrated pharmacovigilance and medicines information activities to capitalize on the potential synergy between the two areas and to leverage scarce resources. The launch of the Therapeutics Information and Pharmacovigilance Center (TIPC) in 2008 introduced broad-based medicine safety information services to health care providers and the public.

To establish the TIPC, SPS first specified the elements needed to build institutional capacity for medicine safety monitoring, including structures, systems, stakeholder roles and responsibilities, staff skills, infrastructure, and tools. For example, Namibia institutionalized the TIPC by placing it under the Namibia Medicine Regulatory Council. Newly established expert committees, such as the clinical committee and DTCs, serve as the TIPC's advisory body and decentralized units, respectively. This organizational structure facilitates sustainability of the center. SPS also drafted national guidelines and standard operating procedures for the center, provided

access to medicine information databases and other resources, and initiated the publication of the center's bulletin—*The Namibia Medicine Watch*.

SPS has helped the MoHSS build capacity in medicine information and safety: from the launch in May 2008 to April 2009, the center processed 98 ADR reports (49 reports per million people per year, 86 percent of which are related to ARVs), handled 107 therapeutics inquiries, and trained about 150 health care workers on medicine safety. Recently, MoHSS identified zidovudine-associated anemia as the priority medicine safety issue for the ART program and asked SPS to support active surveillance of zidovudine use. Namibia is now an official member of the WHO International Drug Monitoring Program and is pursuing efforts to join the International Society of Drug Bulletins. The TIPC is now bridging a gap and providing valuable services to the health system. Health care workers, public health program managers, and patients now have a reliable place to go for information to improve treatment and outcome; expert committees have a resource for revising treatment guidelines and essential medicine lists; and the Namibia Medicine Regulatory Council now has access to safety data to make informed regulatory decisions.

collecting reports from health professionals around the country. More 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); for example, Vietnam plans to establish three regional centers coordinated by a national drug information and adverse drug reaction monitoring center. In addition, Namibia created synergy by creating a national center responsible for both medicines information and pharmacovigilance activities (box 2).

Pharmacovigilance in 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 public health system (for example, HIV/AIDS, tuberculosis, malaria, vaccinations). Vertical treatment initiatives depend on good pharmacovigilance practices (WHO 2006); monitoring ADRs is especially important when treatment is being scaled up, such as ART for HIV/AIDS, or if the standard treatment guidelines change, such as the switch to ACTs 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 and integrated. In some cases, the country may not have a national pharmacovigilance system, in which 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, SPS helped individual ART programs institute site-based ADR monitoring as they scaled up their treatment programs; 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.

Pharmacovigilance at the International Level

Internationally, WHO, through its collaboration with *the* Uppsala Monitoring Centre, has created a global network to share data and information about the benefits and risks of medicinal products. This network includes a common database, to which participating members can contribute medicine safety data, such as ADEs. The network membership has grown to include almost 100 countries, including many developing countries.

Capacity Building for Pharmacovigilance

The SPS Program works with countries to build in-country capacity to institute a pharmacovigilance system using the conceptual framework in figure 3. The framework illustrates the need to address health structures, systems, and roles; staff

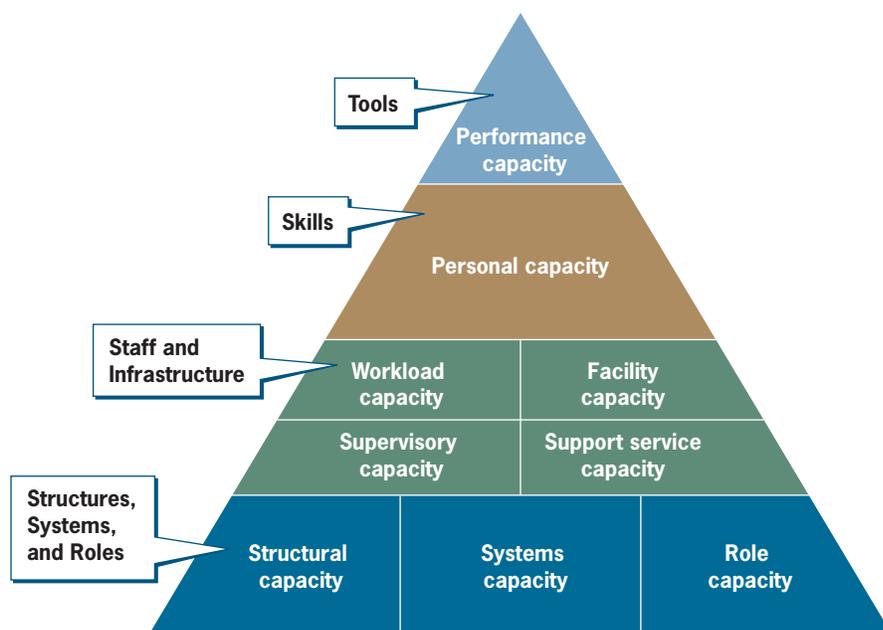


FIGURE 3.
Building capacity for
pharmacovigilance

Adapted from Potter and
Brough 2004

and infrastructure; skills; and tools to effectively provide medicine safety services. Box 3 provides an example.

Building capacity for a comprehensive pharmacovigilance system involves—

- Developing a functional and sustainable regulatory and organizational structure, operational plan, and guidelines for pharmacovigilance and medicine safety monitoring
- Clearly defining the roles and responsibilities of expert advisory committees, DTCs, public health programs, hospitals and clinics, health care providers and professional associations, academic institutions, pharmaceutical manufacturers, importers, wholesalers and retailers, consumers, and media
- Assuring that infrastructure and staffing needs are fulfilled (starting with the national pharmacovigilance center)
- Helping pharmacovigilance personnel build new skills and competencies (e.g., clinical pharmacy, active surveillance methods)
- Institutionalizing appropriate tools (e.g., standard operating procedures, reporting and communication forms, job aids) to support improved data collection, analysis, and reporting

Developing Structural Capacity

The medicine regulatory authority’s most important role is to lead the collaboration among the various pharmacovigilance partners and to assure that information feedback loops are working. An important coordination function is to monitor performance and create a culture of responsibility in the system, whereby every partner knows his or her role and what is expected.

BOX 3. SUPPORTING PHARMACOVIGILANCE IN SOUTH AFRICA

At the request of the Directorate of Pharmaceutical Services of KwaZulu Natal (KZN), SPS helped the province develop a framework to implement an ADR monitoring and reporting program for ARVs and related medicines. RPM Plus assessed the infrastructural and informational needs of health care workers to carry out the program and helped provincial staff develop an ADR reporting form, data collection tools, and an automated system to manage and assess data.

With support from several partners, KZN developed a successful Global Fund proposal to conduct an active ARV surveillance program comprising a sentinel site surveillance program and a cohort event monitoring program. KZN asked SPS to help develop and implement the program at 14 sentinel sites and 8 cohort sites, including developing the study protocol and manual, implementing a data management system and reporting tools, training study investigators and site staff, and establishing a data analysis framework. A total of 280 persons from all 22 sites have been trained. SPS also participates in a provincial pharmacovigilance steering committee that supports implementation at study sites.

The sentinel site surveillance program complements KZN's existing ADR reporting system for ART patients by focusing on surveillance and reporting of medicine-medicine interactions, interactions with traditional medicines, medication errors, and other previously unmonitored medicine-related toxicities. The objective of the provincial cohort event monitoring program is to collect long-term data on safety and treatment outcomes in ART patients. SPS also helps analyze and assess ADR reports related to ART regimen changes from all sites in the province. This ADR database provides important information on toxicity-related treatment switches and is unique because it includes systematically collected data on all regimen changes in the province. As a result of this intervention, WHO invited KZN to collaborate with its HIV cohort event monitoring program.

SPS is also helping the national tuberculosis program develop a framework for focused surveillance of multi- and extensively drug-resistant tuberculosis treatment-related ADRs at sentinel sites in several provinces.

As mentioned above, pharmacovigilance partners may include pharmaceutical procurement officials, professional organizations, media outlets, patient and caregiver advocacy groups, and public health program managers, in addition to health care managers at the facility, district, regional, and national levels. Establishing linkages and widely disseminating medicine safety information builds decision-making capacity as evidenced in Namibia (box 4).

Another key component of developing a strong system is the integration of pharmacovigilance activities of public health programs, such as HIV/AIDS treatment and childhood immunizations, into the national pharmacovigilance system. Multiple ADR reporting structures tend to evolve when a country has vertical public health programs operating; however, such fragmentation ultimately weakens the system. Conversely, a public health program that has a well-established ADR collection and reporting structure can serve as a model and a starting point for a national system, if one does not already exist.

Developing Staff Capacity

Medication safety is a concept that everyone understands. The key is to make people—from regulators to health care providers and consumers—realize that everyone has a role to play in helping to make medicines safer. Pharmacovigilance

BOX 4. ESTABLISHING LINKAGES FOR DECISION MAKING IN NAMIBIA

In 2007, Namibia changed the backbone of its recommended first-line ART from stavudine to zidovudine because of concerns about peripheral neuropathy, but the country lacked any local safety data to support the decision. In 2008, surveillance from the newly established national TIPC indicated that zidovudine-associated anemia was the most frequently reported ARV adverse effect (64 percent). Such findings provide objective evidence on the

benefits and risks associated with current treatment regimens, which should support future decisions on ART recommendations. Therefore, establishing a regular communication channel between the TIPC and the National AIDS Control Council to facilitate the use of local pharmacovigilance information is imperative, and this information needs to be used to develop and update treatment guidelines to benefit the local population.

topics should be part of the curricula for health care professionals, both preservice and in-service, and the medicine regulatory authority should make sure that pharmacovigilance training materials are harmonized nationwide (box 5).

All health care providers, including physicians, pharmacists, nurses, dentists, and others, should realize that reporting ADRs and medication errors is part of their professional responsibility. Voluntary reporting of ADRs and medication errors requires health care providers to be active participants in a culture of safety. Even though programs relying solely on voluntary, spontaneous reporting methods reveal only the tip of the iceberg, voluntary reporting should always be encouraged, because it helps to establish a team approach to improving patient care and reducing risks. Nonetheless, under-reporting is a common challenge in all pharmacovigilance systems at the facility, regional, or national level. Barriers to reporting ADRs to the medicine regulatory authority or the national pharmacovigilance center include a—

- Lack of awareness by health care professionals of the importance of ADR reporting
- Low percentage of staff trained in pharmacovigilance
- Lack of priority setting within the medicine regulatory authority and public health programs—pharmacovigilance is not emphasized enough
- Lack of technical and financial resources at the facility to collect and analyze the data
- Weak organizational structure at the medicine regulatory authority, leading to uneven distribution and collection of ADR forms from health facilities
- Lack of regular follow-up and supervision by the pharmacovigilance coordinator at the medicine regulatory authority

Supervisory visits that reinforce proper procedures and a feedback loop that assures that health care providers know that their efforts are meaningful and acted on increase the level of reporting in a pharmacovigilance system. Data reporters need to feel that the reports will not reflect negatively on their institutions and that

BOX 5. SPS WORKS WITH THE PHARMACY AND POISONS BOARD TO DEVELOP STANDARDIZED TRAINING MATERIALS

In mid-2007, Kenya's medicine regulatory authority, the Pharmacy and Poisons Board (PPB), launched a pharmacovigilance program that instituted voluntary reporting of ADRs to all medicines. The government developed national guidelines and reporting tools and conducted a national sensitization workshop for pharmacists, pharmaceutical technologists, clinicians, clinical officers, and nurses from all the country's provinces. Health care sector stakeholders emphasized the need to create a standard health care worker training approach and tools to ensure the uniform communication of key messages. Furthermore, the Ministry of Health embraced the concept of

standardized curricula for a range of public health programs, including the National AIDS & STI Control Programme, Division of Reproductive Health, and Division of Malaria Control.

As part of its rollout of the national pharmacovigilance program, the PPB proposed developing a standard curriculum for training health workers on pharmacovigilance. SPS worked with the PPB to develop the standardized curriculum and tools through a series of stakeholder workshops, held in July and August 2008.

their reports are important, even if they have some doubt about the causal role of the medication in question.

The medicine regulatory authority and pharmacovigilance center can build awareness among different stakeholders through training and outreach. Outreach activities may include communicating with professional groups (e.g., professional organization newsletters), health care providers in-service (e.g., a lunch-time seminar), and the public (e.g., billboards about the dangers of counterfeit medicines). Involving the media is a good way to reach everyone who reads a newspaper or listens to the radio—which includes health care providers, policy makers, and patients.

SPS Operational Approach

Although pharmacovigilance activities often operate on a limited scale, such as involving only one public health program or including only voluntary ADR reporting, the SPS Program emphasizes a comprehensive, systems-oriented approach to pharmacovigilance. SPS works with countries to develop an operational strategy that encompasses the full spectrum of medicine safety—product quality, ADRs, and medication errors—using a range of surveillance methods, including active surveillance. Countries can then implement the system in phases as they build capacity and establish necessary resources. A strategy that enables different development partners to provide technical or financial support to capacitate discrete components of the national pharmacovigilance system can be one approach for moving forward. SPS's work with the government of Vietnam provides a good example of this approach (box 6).

The responsibility for pharmacovigilance should be shared among multiple stakeholders, including drug regulators, the pharmaceutical industry, WHO,

public health programs, academic researchers, donor organizations, the health care delivery sector, and the public and patients (Pirmohamed et al. 2007). In practice, such interactions among stakeholders have been limited and fragmented. One of the SPS Program's key areas of technical assistance is to help countries map all stakeholder roles and responsibilities in the system and bring stakeholders together to address pharmacovigilance as a common issue. This collaborative approach creates synergy and better coordination in creating and sustaining advocacy and actions that support pharmacovigilance. The actual process of developing a framework to establish or strengthen a pharmacovigilance system can also facilitate coordination among stakeholders. As part of a collaborative effort, partners can identify gaps and duplication, successes and strengths to build on, and opportunities for streamlining and harmonizing roles and responsibilities.

BOX 6. A PHASED EXPANSION OF VIETNAM'S PHARMACOVIGILANCE SYSTEM

The government of Vietnam recognizes the need for and importance of a functioning national system for monitoring and taking measures to prevent ADRs and for providing pharmaceutical information to policy makers, health care providers, and consumers. Under law, medical professionals and establishments, manufacturers, and distributors are required to report ADRs to the heads of their organizations and to the medicine regulatory authority. Furthermore, the Minister of Health is responsible for organizing systems for providing pharmaceutical information and monitoring of ADRs to assure the safe and effective use of medicines.

The government assigned the Ministry of Health's Drug Administration Department and the Hanoi University of Pharmacy the responsibility of establishing a National Drug Information and Adverse Drug Reaction (DI-ADR) Monitoring Center, which serves as the hub or central unit for Vietnam's pharmacovigilance system. As the two implementing partners move forward to set up the National DI-ADR Monitoring Center plus three other proposed regional centers in northern, central, and southern Vietnam, SPS is working with stakeholders to review the scope of existing pharmacovigilance activities, identify priorities in taking a systems approach, and developing consensus on what role stakeholders should play and how to implement a fully functioning pharmacovigilance system.

In Vietnam, pharmacovigilance activities have historically been conducted through a passive approach, dependent on health worker suspicions and reporting of potential adverse reactions to medicines. Lessons learned from other countries suggest that active approaches and formal research methods are also needed to evaluate potential problems and provide measures of the level of potential risk. SPS recommended that the pharmacovigilance system incorporate active surveillance methods, including the use of registries, sentinel sites, and follow-up of patient cohorts. SPS also suggested that reports made to the new DI-ADR Center should include pharmaceutical product defects and medication errors, in addition to ADRs.

Building a functioning and effective pharmacovigilance system that is sustainable in the long term will likely require implementation to be phased in over a number of years because of capacity and financial constraints. In addition, technical and financial inputs will probably be needed from a number of development partners in addition to the existing and planned inputs from the Government of Vietnam. Based on their areas of interest, development partners may choose to support specific pharmacovigilance activities, such as product quality; individual partner organizations, such as the National DI-ADR Monitoring Center; or a particular disease or program or group of pharmaceuticals, for example, ARVs. The Government of Vietnam may also submit a proposal to the Global Fund to support pharmacovigilance system strengthening for a number of key components.

To achieve the objectives of a pharmacovigilance system, the SPS operational approach comprises the following steps—

- **Assess the existing pharmacovigilance system.** Work with partners to assess the status of pharmacovigilance systems and diagnose the system's strengths, weaknesses, and gaps using a pharmacovigilance assessment methodology. The assessment covers all aspects of the pharmacovigilance framework: people, functions, and structures.
- **Develop a customized system improvement model.** Using the results of the assessment, SPS works with in-country stakeholders to identify and analyze options and develop relevant, feasible, and sustainable approaches that are customized to the country's existing regulatory capacity and priorities, system gaps, and resource availability. SPS also works with national partners to identify appropriate interventions to implement at various levels, such as the health facility level, public health program level, national level, and even potentially at a regional level through inter-country collaboration.
- **Help implement the identified interventions.** SPS works with in-country stakeholders, collaborating partners, and other USAID-funded projects to help prioritize and carry out the identified interventions.
- **Monitor and evaluate medicines safety activities.** SPS provides technical assistance to in-country partners to develop and implement an indicator-based monitoring program for their pharmacovigilance system.

Unlike the experience in Vietnam of building on an existing system, SPS's work in Rwanda provides a good example of the challenges associated with creating a pharmacovigilance system from the ground up (box 7).

In summary, the use of pharmaceuticals involves a trade-off between their benefits and the potential for harm. Pharmacovigilance can help minimize the risk of harm by ensuring that medicines of good quality are used appropriately and that health care providers and consumers have the information they need to make knowledgeable decisions about treatment. Countries can create a comprehensive medicine safety system through careful strategic planning that encompasses all aspects of pharmacovigilance, but uses phased implementation, and effectively coordinated technical and financial support to achieve long-term goals.

BOX 7. STARTING AT THE BEGINNING: ESTABLISHING A PHARMACOVIGILANCE AND MEDICINE INFORMATION SYSTEM IN RWANDA

The SPS Program has been working with Rwanda's Pharmacy Task Force (PTF) and other stakeholders to develop a broad-based medicine safety system from scratch, including establishing the National Pharmacovigilance and Medicines Information Center. Stakeholders have defined the functions of the planned comprehensive system in the document, "Strategic Approach for the Establishment of a Pharmacovigilance System in Rwanda"—

- Monitor safety of medicines used in Rwanda
- Quantify and characterize occurrence of previously recognized ADRs in Rwanda
- Conduct and coordinate spontaneous reporting and active surveillance activities
- Determine real-life effectiveness of medicines used in Rwanda
- Provide unbiased medicine information to health workers and consumers
- Monitor the promotion and advertising of all health products
- Improve rational use of medicines
- Improve patient safety
- Develop interventions to reduce medicine-related morbidity and mortality

One of the biggest challenges is finding an appropriate administrative home for the pharmacovigilance system; often a country's medicine regulatory authority will take that responsibility, but Rwanda does not have such an authority. The PTF is the likely candidate, but because of its limited capacity, public health programs such as HIV/AIDS, tuberculosis, and malaria will need to provide support. The strategy also gives DTCs a key role in decentralizing Rwanda's pharmacovigilance system. Since 2007, SPS has helped the PTF establish DTCs in about 18 district hospitals to help improve medicine use. SPS continues to work with the PTF to create a national DTC to oversee update of standard treatment guidelines, national formulary, and essential medicines list and to coordinate hospital-level DTC activities.

To get things started in Rwanda, SPS carried out the following steps—

- Organized and conducted a stakeholder workshop to advocate for the establishment of a pharmacovigilance system in Rwanda. At the workshop—
 - Set up a technical working group to follow up on stakeholder recommendations
 - Designed the pharmacovigilance system and drafted a one-year work plan
- Developed technical documents and tools to set up and run the system, including guidelines, terms of reference, ADR notification form, patient alert card, and medicines information request form; field-tested the ADR notification form in all levels of the health care system
- Developed a pharmacovigilance training curriculum, including a training-of-trainers component, to implement a cascade training plan
- Initiated contacts with *the* Uppsala Monitoring Centre regarding Rwanda's membership in the international drug safety network
- Trained local staff from PTF, the National University of Rwanda, and SPS in pharmacovigilance

Next steps will include launching the National Pharmacovigilance and Medicines Information Center; conducting training for trainers, DTC representatives, and hospital and health center staff; disseminating guidelines and tools to implementers at all levels; initiating ADR reporting and notification activities and some active surveillance activities in partnership with the Center for Treatment and Research on AIDS and the maternal-child health program; and establishing a medicine information system within the National Pharmacovigilance and Medicines Information Center.

References

- Agiro, E. 2009. "Malaria Injections Cripple 45 Children." *The New Vision*, Kampala Uganda. May 23, 2009.
- Atemnkeng, M. A., K. De Cock, and J. Plaizier-Vercammenn. 2007. "Quality Control of Active Ingredients in Artemisinin-Derivative Antimalarials within Kenya and DR Congo." *Tropical Medicine and International Health* 12(1): 68–74.
- Aspden, P., J. Wolcott, J. L. Bootmann, and L. R. Cronenwett. (eds.). 2006. *Preventing Medication Errors*. Washington, D.C.: National Academy Press, Institute of Medicine Committee on Identifying and Preventing Medication Errors.
- Barker, K. N., E. A. Flynn, G. A. Pepper, et al. 2002. "Medication Errors Observed in 36 Health Care Facilities." *Archives of Internal Medicine* 162: 1897–1903.
- Bate, R., P. Coticelli, R. Tren, and A. Attaran. 2008. "Antimalarial Drug Quality in the Most Severely Malarious Parts of Africa—A Six Country Study." *PLoS ONE* 3(5): e2132.
- Dellicour, S., S. Hall, D. Chandramohan, and B. Greenwood. 2007. "The Safety of Artemisinins during Pregnancy: A Pressing Question." *Malaria Journal* 6: 15.
- Ferner, R. E. and J. K. Aronson. 2006. "Clarification of Terminology in Medication Errors—Definitions and Classification." *Drug Safety* 29(11): 1011–22.
- The Global Fund to Fight AIDS, Tuberculosis and Malaria. 2009. "Distribution of Funding after 7 Rounds." <http://www.theglobalfund.org/en/distributionfunding/?lang=en>.
- ISMP (The Institute for Safe Medication Practices). 2008. "Heparin Errors Continue Despite Prior, High-Profile, Fatal Events." *ISMP Newsletter*, July 17, 2008. <http://www.ismp.org/Newsletters/acute/ articles/20080717.asp>.
- Kohn, L. T., J. M. Corrigan, and M. S. Donaldson (eds.). 1999. *To Err is Human: Building a Safer Health System*. Washington, D.C.: National Academy Press, Institute of Medicine. <http://www.nap.edu/books/0309068371/html/>.
- Lazarou, J., B. Pomeranz, and P. Corey. 1998. "Incidence of Adverse Reactions in Hospitalized Patients: A Meta-analysis of Prospective Studies." *Journal of the American Medical Association* 279(15): 1200–05.
- Naranjo, C., et al. 1981. "A Method for Evaluating the Probability of Adverse Drug Reactions." *Clinical Pharmacology Therapeutics* 30: 239–45.
- NCC MERP (National Coordinating Council for Medication Error Reporting and Prevention). 2009. "About Medication Errors." <http://www.nccmerp.org/aboutMedErrors.html>.
- Nebeker, J. R., P. Barach, and M. H. Samore. 2004. "Clarifying Adverse Drug Events: A Clinician's Guide to Terminology, Documentation, and Reporting." *Annals of Internal Medicine* 140: 795–801.
- O'Brien, K. L., J. D. Selanikio, C. Hecdivert, et al. 1998. "Epidemic of Pediatric Deaths from Acute Renal Failure Caused by Diethylene Glycol Poisoning." *Journal of the American Medical Association* 279(15): 1175–80.
- Onwujekwe, O., H. Kaur, N. Dike, et al. 2009. "Quality of Anti-malarial Drugs Provided by Public and Private Healthcare Providers in South-east Nigeria." *Malaria Journal* 8: 22.
- Pirmohamed, M., K. N. Atuah, A. N. O. Doodoo, and P. Winstanley. 2007. "Pharmacovigilance in Developing Countries." *British Medical Journal* 335: 462.
- Potter, C. and R. Brough. 2004. "Systematic Capacity Building: Hierarchy of Needs." *Health Policy and Planning* 19(5): 336–345.
- Rentz, E. D., L. Lewis, O. J. Mujica, et al. 2008. "Outbreak of Acute Renal Failure in Panama in 2006: A Case-Control Study." *Bulletin of the World Health Organization* 86: 749–56.
- Ward, S. A., E. J. P. Sevens, I. M. Hastings, et al. 2007. "Antimalarial Drugs and Pregnancy: Safety, Pharmacokinetics and Pharmacovigilance." *Lancet Infectious Disease* 7(2): 136–44.
- WHO. 2002. *The Importance of Pharmacovigilance: Safety Monitoring of Medicinal Products*. Geneva: WHO. <http://whqlibdoc.who.int/hq/2002/a75646.pdf>.
- . 2006. *The Safety of Medicines in Public Health Programmes: Pharmacovigilance an Essential Tool*. Geneva: WHO.
- WHO/UMC (the Uppsala Monitoring Centre). 2000. *Safety Monitoring of Medicinal Products: Guidelines for Setting up and Running a Pharmacovigilance Centre*. Uppsala, Sweden: the Uppsala Monitoring Centre.
- WHO and MMV (Medicines for Malaria Venture). 2009. *Pharmacovigilance Guidance for Countries Participating in AMFm Phase I*. WHO-MMV Joint Technical Consultation on Active Pharmacovigilance Monitoring with a Special Focus on AMFm. Conference proceedings from International Center, Cointrin, Geneva, April 4–6, 2009. Geneva: WHO.

Acknowledgments

SPS would like to gratefully acknowledge the contributions of the following individuals and organizations in writing and reviewing this document.

Contributors

Shabir Banoo, SPS Program, South Africa
Martha Embrey, Center for Pharmaceutical Management, US
Mohan Joshi, SPS Program, US
Douglas Keene, SPS Program, US
David Lee, Center for Pharmaceutical Management, US
Jude Nwokike, SPS Program, US

Catherine Corbell, University of Washington, US
Andy Stergachis, University of Washington, US

Alexander Dadoo, Centre for Tropical Clinical Pharmacology &
Therapeutics, Ghana

Reviewers

Niranjan Konduri, Center for Pharmaceutical Management, US
Negussu Mekonnen, SPS Program, Ethiopia
Sue Putter, SPS Program, South Africa
Rima Shretta, SPS Program, US
Helena Walkowiak, SPS Program, US

Strengthening Pharmaceutical Systems

Center for Pharmaceutical Management

Management Sciences for Health

4301 North Fairfax Drive, Suite 400

Arlington, VA 22203 USA

Telephone: 703.524.6575

Fax: 703.524.7898

E-mail: sps@msh.org

Web: www.msh.org/sps



Management Sciences for Health, an international nonprofit organization, uses proven approaches developed over four decades to help leaders, health managers, and communities in developing nations build stronger health systems for greater health impact.

