

## **Pharmacovigilance in Rwanda: A Systems Analysis**

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## **Abstract**

The Rwanda Ministry of Health is leading current efforts to establish a broad-based medicine safety surveillance system. Such a system will have the capacity for conducting pharmacovigilance, medicine information, and patient safety activities. The Indicator-Based Pharmacovigilance Assessment Tool was used to assess the current capacity of the pharmacovigilance system to meet these expectations. The baseline data generated informed recommendations for improving Rwanda's capacity for pharmacovigilance and medicine safety activities.

## **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.

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## **Key Words**

pharmacovigilance, medicine safety, surveillance, capacity building

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## ACRONYMS

ACT	artemisinin-based combination therapy
ADR	adverse drug reaction
ART	antiretroviral therapy
CHW	community health worker
IPAT	Indicator-Based Pharmacovigilance Assessment Tool
MSH	Management Sciences for Health
NPMIC	National Pharmacovigilance and Medicine information Center
PNILP	National Integrated Program to Fight Malaria
PTF	Pharmacy Task Force
SOP	standard operating procedure
SPS	Strengthening Pharmaceutical Systems
TOT	training of trainers
TB	tuberculosis
UMC	WHO Collaborating Center for International Drug Monitoring in Uppsala, Sweden
WHO	World Health Organization



## BACKGROUND

There is no complete understanding of the safety of new medicines at the point of registration. Data on the safety of new medicines are mainly derived from preauthorization clinical trials in controlled settings. Clinical trials for the evaluation of safety and efficacy are conducted in a limited number of patients with strict inclusion criteria, often excluding special patient groups such as those with comorbid conditions, children, the elderly, and pregnant women. Patients often have no long-term exposure to the product during clinical trials, and the new drug may not have been tested in some racial groups who may end up using the medicines. These limitations of preauthorization clinical trials enforce the importance of monitoring the safety of all medicines. Besides the discovery of new medicine-induced disorders, including rare and serious adverse drug reactions (ADRs) that were not known during clinical trials, monitoring the safety of health products postauthorization can provide useful information for the characterization and quantification of prevalence and risk factors of known ADRs and can warn of cases of counterfeit products. The need for more scrutiny of the safety of health products is well recognized in developed countries. Increasingly, in developing countries, the importance of pharmacovigilance is also being recognized. One of the key factors for this recognition is the increased availability of new essential medicines used in mass treatment health programs like antiretroviral therapy (ART), tuberculosis (TB), malaria, and vaccination programs. The World Health Organization (WHO) defines *pharmacovigilance* as the science and activities relating to the detection, evaluation, understanding, and prevention of adverse reactions to medicines or any other medicine-related problems.<sup>1</sup> Pharmacovigilance or postmarketing surveillance is crucial to quantify previously recognized ADRs, identify unrecognized adverse drug events, and evaluate the effectiveness of medicines in real-world situations as well as to decrease mortality and morbidity associated with adverse events.<sup>2</sup>

In many countries, national drug authorities are responsible of ensuring the quality, safety, and efficacy of medicines in the public and private sectors. Rwanda currently does not have a drug regulatory authority. However, the recently established Pharmacy Task Force (PTF) is currently addressing some of the regulatory activities of drug regulatory authorities. The PTF is responsible for the protection of the population by supervising the effectiveness and the quality of pharmaceutical products and ensuring they are available at national level and appropriately used.<sup>3</sup> The PTF has made some efforts to initiate pharmacovigilance activities. In addition, the public health programs in Rwanda have recently indicated interest in monitoring the safety of medicines used in their programs. The Treatment and Research AIDS Center and the National Integrated Program to Fight Malaria (PNILP) are concerned about the need to establish an ADR reporting system given the lack of long-term experience in the use of the current treatment.

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<sup>1</sup> World Health Organization. 2002. *The Importance of Pharmacovigilance: Safety Monitoring of Medicinal Products*. Geneva: WHO.

<sup>2</sup> Egualé, T., et al. 2008. Detection of adverse drug events and other treatment outcomes using an electronic prescribing system. *Drug Safety* 31(11):1005–16.

<sup>3</sup> Ministry of Health. Pharmacy Task Force.

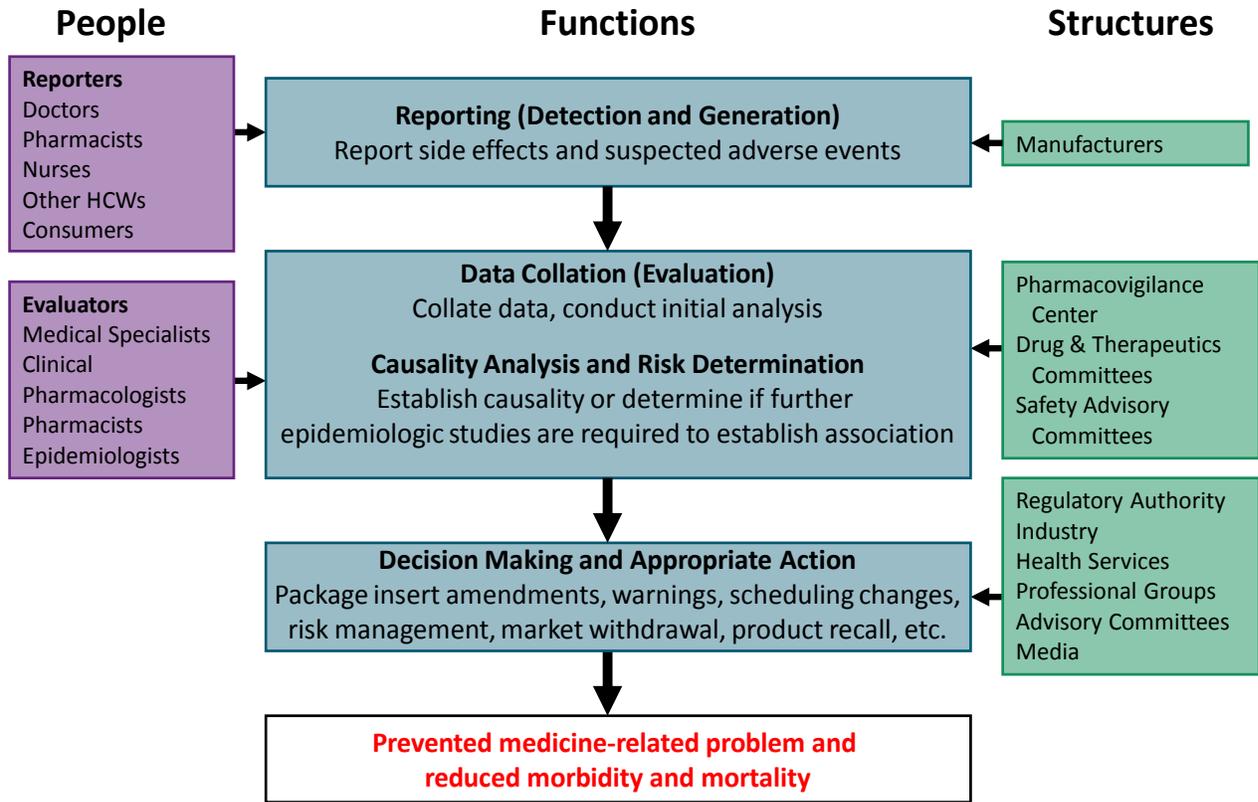


## CAPACITY BUILDING FOR PHARMACOVIGILANCE

The Rwanda Ministry of Health through the PTF developed strategies and plans for the establishment of broad-based pharmacovigilance and medicine safety activities. Rwanda is desirous of a system that facilitates the implementation of a whole spectrum of pharmacovigilance, drug information, and patient safety activities. Management Sciences for Health's Strengthening Pharmaceutical Systems (MSH/SPS) Program was asked to assess Rwanda's current situation. The PTF hopes the assessment findings will provide guidance to ongoing and future efforts to develop a comprehensive pharmacovigilance and medicine safety system.

Currently, no performance monitoring tool exists for assessing where a country stands in achieving a functional pharmacovigilance system. MSH/SPS has a newly developed Indicator-Based Pharmacovigilance Assessment Tool (IPAT) that will be useful for addressing this gap and in the diagnostic assessment of pharmacovigilance systems in developing countries. IPAT supports evidence-based options analysis and development of relevant and feasible recommendations reflecting each country's local realities, existing regulatory capacity and priorities, identified system gaps, and resource availability. Additionally, the standardized and indicator-based approach included in the tool allows longitudinal measurement of progress after the recommended interventions are implemented. The tool assesses a country's overall capacity for medicine safety, therapeutic ineffectiveness, and pharmaceutical product quality issues. A medicine safety system is the coordinated and interdependent functioning of activities to improve benefits and reduce harm related to the use of health products by the public through the efficient mobilization of people, functions, and structure at all levels and in all sectors. Figure 1 depicts a pharmacovigilance framework that articulates the interconnection between people, functions, and structures to ensure an integrated and comprehensive pharmacovigilance and medicine safety system. Components of this framework are covered by what the IPAT assesses.

# The Pharmacovigilance Framework



Source: Strengthening Pharmaceutical Systems (SPS). 2009. *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.

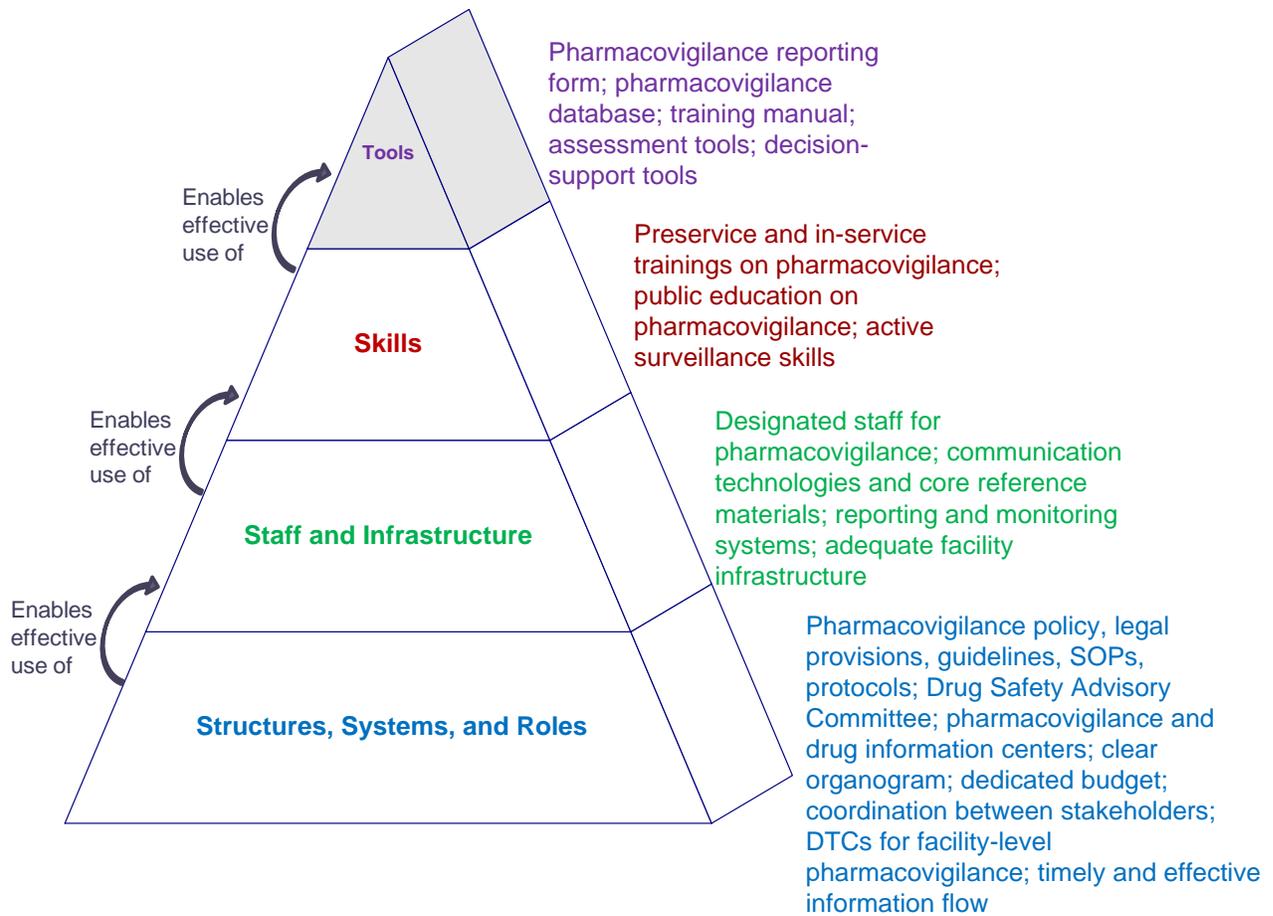
Note: HCWs = health care workers.

**Figure 1. The Pharmacovigilance Framework**

In Rwanda, the development, establishment, functioning, and sustainability of such a comprehensive medicine safety system, as articulated by the illustrated framework, require the building of institutional capacities. *Capacity building* is the creation of an enabling environment with appropriate policy and legal frameworks; institutional development, including community participation; human resources development; and strengthening of managerial systems.<sup>4</sup> Capacity building for medicine safety monitoring therefore should address all processes for the development of individual and system capacity and enable Rwanda to achieve the sustainable ability to manage effectively the safety of patients and health products in the country. According

<sup>4</sup> Urban Environmental Management Web site. Urban Capacity Building, Defining Capacity building. <http://www.gdrc.org/uem/capacity-define.html>. Accessed January 24, 2009.

to Potter and Brough,<sup>5</sup> capacity building should enable program execution independent of changes of personalities, technologies, social structures, and resource crises. That is, it should imply developing sustainable, and robust, systems. Capacity building can be achieved through applying a four-tier hierarchy of capacity-building needs: structures, systems, and roles; staff and infrastructure; skills; and tools. Figure 2 depicts the pharmacovigilance capacity-building pyramid that describes the related elements for achieving a fully functional and sustainable medicine safety system.



Source: Adapted from Potter, C., and R. Brough. 2004. Systemic capacity building: A hierarchy of needs. *Health Policy Planning* 19:336–45.

**Figure 2. Capacity-building model for pharmacovigilance**

<sup>5</sup> Potter, C., and R. Brough. 2004. Systemic capacity building: A hierarchy of needs. *Health Policy Planning* 19:336–45.

## **The Indicator-Based Pharmacovigilance Assessment Tool**

IPAT is a comprehensive performance metric to monitor and evaluate pharmacovigilance and the medicine safety system. IPAT has 43 indicators—26 core and 17 supplementary—that address five pharmacovigilance and medicine safety system components: (a) policy, law, and regulation; (b) systems, structures, and stakeholder coordination; (c) signal generation and data management; (d) risk assessment and evaluation; and (e) risk management and communication. The indicators are also classified by “structural,” “process,” or “outcome,” according to the product or result they measure. IPAT is modular; different segments of the health system can pull out indicators relevant to them to monitor different medicine safety issues. The process for the development of the IPAT included literature review to identify published and unpublished indicators. Results identified 15 relevant reports with approximately 200 indicators addressing areas ranging from regulatory pharmacovigilance to medication safety. The identified indicators were aligned with key pharmacovigilance components, and new indicators were proposed to address gaps. The first list of candidate indicators was subjected to explicit criteria to assess them for objectivity, reliability, relevance or adequacy, measurability, validity, and practicability. The 88 candidate indicators were presented in three rounds of Delphi consultations, which involved exploring and distilling the opinions of pharmacovigilance experts in an iterative process. The Delphi group, with 12 respondents in eight countries, generated 27 responses. The group members weighted the indicators based on whether they considered them “core” or “supplementary.” The indicators chosen by the Delphi group were used to formulate relevant assessment questions, and the group then reviewed those questions.

## **Assessment Methods**

The objective was to conduct a diagnostic assessment of Rwanda’s existing pharmacovigilance system using the indicator-based pharmacovigilance assessment tool developed by SPS. The methods for this rapid assessment included—

- Document review.
- Structured interviews using the assessment questions in IPAT: A total of 93 assessment questions were used for data collection. The data collection sites included five national departments or programs and 16 health facilities in eight regions.
- Key informant interviews.
- Additional feedback from respondents to address other locally relevant issues or questions. Respondents could also suggest new indicators they consider locally relevant.

The data obtained were input to a master sheet and analyzed. Overall system status was assessed based on analysis of strengths, weaknesses, and opportunities. This analysis was then used as the

basis for providing prioritized recommendations taking into account the local context and realities. The assessment method is described in more detail in a trip report.<sup>6</sup>

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<sup>6</sup> Nwokike, J., and M. Joshi. 2009. *Assessment of Pharmacovigilance and Medicine Safety System in Rwanda*. Submitted to the U.S. Agency for International Development by the Strengthening Pharmaceutical Systems (SPS) Program. Arlington, VA: Management Sciences for Health.



## ASSESSMENT FINDINGS, ANALYSIS, AND RECOMMENDATIONS FOR IMPROVING THE PHARMACOVIGILANCE SYSTEM IN RWANDA

### Analysis Format

The findings from the assessment were reviewed taking into consideration the five pharmacovigilance components. Under each component, the findings were used to determine how Rwanda measures up to a fully functional pharmacovigilance system. The pharmacovigilance framework and the capacity-building model were then considered to inform recommendations for immediate and future priority interventions.

### ***Policy, Law, and Regulation***

Existence of a pharmacovigilance policy indicates that a country has accorded high-level attention and commitment to improving medicine safety and helps provide a broad direction to advance the cause. Similarly, existence of relevant legislation and regulations provides a framework that mandates certain compliance by relevant parties and stakeholders and gives a legal basis for monitoring and action.

The findings from the assessment show that Rwanda is attempting to build policy, law, and regulations for the implementation of a medicine safety system. It has drafted a National Medicine Policy that includes pharmacovigilance as a subset. IPAT assesses whether policies and guidelines of public health programs contain statements on monitoring safety of medicines used in those programs. The Rwanda community health worker (CHW) program is a model in that respect. The ministry of health guidelines for the implementation of the community health program<sup>7</sup> clearly outlined commitments to monitor safety of medicines used in the program and even contains an implementation plan for addressing this commitment.

A Food and Drug Act has just been drafted with sections that address pharmacovigilance. However, the full details of what is proposed for addressing pharmacovigilance in the act was not reviewed during the assessment. One major constraint Rwanda is currently facing is that the Food and Drug Act has not been promulgated. Therefore, to date, no legal mandate and backing supports pharmacovigilance activities in the country. Table 1 identifies the impact of the absence of these fundamental aspects of pharmacovigilance system.

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<sup>7</sup> Ministère de la Santé Unité Politiques et Développement des Capacités Desk Santé Communautaire. *Guide de mise en oeuvre de la santé communautaire*. November 2007.

**Table 1. Impact of Lack of Policies and Regulations Related to Pharmacovigilance**

Constraints	Impact
No approved policy on pharmacovigilance exists.	Addressing medicine safety is not viewed as obligatory.
Food and Drug Act and related regulation are not in place.	Enforcement is not possible; marketing authorization holders are not required to report ADRs.

Policy, law, and regulation provide the fundamental platform that guides the activities mentioned under the “People,” “Functions,” and “Structures” of a comprehensive pharmacovigilance framework. It will be much less efficient and highly challenging to implement pharmacovigilance activities in Rwanda in the absence of a policy and regulatory framework. Therefore, it is recommended that efforts aimed at establishment of a pharmacovigilance system in Rwanda must address as a first priority the need to put these regulatory instruments in place. The explicit recommendation from the assessment is that Rwanda should immediately finalize and implement pharmacovigilance-related policy, legal provisions, and guidelines.

### **Systems, Structures, and Stakeholder Coordination**

The capacity-building model identifies policy, law, and regulations as part of structures, systems, and roles that are the base of the capacity-building pyramid. These fundamental systems enable effective use of other capacity-building elements. Structures, systems, and roles provide a foundational basis for an organized and systematic operation of pharmacovigilance. They enable or facilitate effective utilization of other elements in the system, such as staff, skills, and tools. A country that has a national pharmacovigilance guideline has a roadmap for conducting pharmacovigilance.

Centers for the provision of medicine information and pharmacovigilance services provide a platform for the coordination of systems for monitoring the safety of health products in a country. The WHO recommends that every country should have a pharmacovigilance center.<sup>8,9</sup> During the assessment, the existence of plans for the establishment of the National Pharmacovigilance and Medicine information Center (NPMIC) at the PTF in the Ministry of Health were identified. The NPMIC will provide pharmacovigilance and medicine information services. Such a joint model already exists in other countries such as Namibia (Therapeutic Information and Pharmacovigilance Center) and Vietnam (National Center of Drug Information and Adverse Drug Reactions). When the NPMIC is formally established, it is expected to significantly strengthen pharmacovigilance in Rwanda by providing unbiased medicine information, monitoring medicine safety and effectiveness, and enhancing rational medicine use. The draft document, *Guidelines for Medicines Safety Surveillance in Rwanda*, was reviewed during the assessment. The document was found to be quite comprehensive. The Rwanda

<sup>8</sup> WHO. 2004. Pharmacovigilance: Ensuring the safe use of medicines. *WHO Policy Perspectives on Medicines* 9. <http://apps.who.int/medicinedocs/pdf/s6164e/s6164e.pdf>.

<sup>9</sup> The Uppsala Monitoring Centre (the UMC), WHO Collaborating Centre for International Drug Monitoring. 2000. *Safety monitoring of medicinal products: Guidelines for setting up and running a pharmacovigilance centre*. Geneva: WHO. <http://apps.who.int/medicinedocs/en/d/Jh2934e/>.

guideline addresses all aspects of safety monitoring of health products, including spontaneous reporting, active surveillance, and control of advertising and promotion of medicines. The document includes roles and responsibilities of different stakeholders, methods of medicine safety surveillance, and guidelines for medicine information. So far, the guideline is not officially published and distributed. Table 2 outlines the impact of the lack of systems, structures, and roles on conducting pharmacovigilance activities in Rwanda.

**Table 2. Impact of Lack of Systems, Structures, and Roles**

<b>Constraints</b>	<b>Impact</b>
National center for monitoring safety of health products and providing unbiased information not in place.	No platform exists for advancing pharmacovigilance and medicine information–related activities; coordinated and system-based pharmacovigilance activities become challenging to implement.
Pharmacovigilance center, guidelines, notification system not yet approved.	Pharmacovigilance activities cannot be formally operationalized.

Once finalized, approved, and distributed, the guidelines will serve as a basis for structured and coordinated actions by various stakeholders in pharmacovigilance. Therefore, it is a priority that the Guidelines for Medicines Safety Surveillance in Rwanda be approved and implemented. A need also exists to develop and implement specific protocols and standard operating procedures (SOPs) to improve medicine safety.

Rwanda is yet to create a multidisciplinary national medicine safety advisory committee. Such a body provides expert technical advice to help guide actions by the pharmacovigilance center and decisions by the regulatory body. A multidisciplinary advisory committee is desirable to support the pharmacovigilance center with regard to the quality of the procedures, including data collection, analysis, and publication.<sup>10</sup> The draft pharmacovigilance guideline has proposed establishment of such a committee (Medicine Safety Committee) and specified its roles and responsibilities.

It is thus recommended that the NPMIC should be established as soon as possible, followed by the Medicine Safety Committee. Existence of an adequately mandated, staffed, budgeted, and functioning pharmacovigilance center can significantly support a medicine safety system by acting as the country’s focal point and coordinating body. The national guidelines will serve as the key tool for the functioning of the NPMIC; it is therefore imperative to finalize the guidelines and begin their implementation.

The responsibility for pharmacovigilance should be shared among multiple stakeholders, including drug regulators, the pharmaceutical industry, the WHO, public health programs, academic researchers, donor organizations, the health care delivery sector, and the public and

<sup>10</sup> the Uppsala Monitoring Centre. 2000. *Safety Monitoring of Medicinal Products: Guidelines for Setting Up and Running a Pharmacovigilance Centre*. <http://apps.w.ho.int/medicinedocs/en/d/Jh2934e/7.4.html>.

patients.<sup>11</sup> Pharmacovigilance is an overarching issue requiring that all stakeholder participation be encouraged and welcomed for successful implementation. However, the experience in many countries is that such interactions among stakeholders have been limited and fragmented. A common understanding and coordinated functioning by these interrelated bodies is imperative for strengthening the pharmacovigilance system. During the current initial period of system building, Rwanda has an opportunity to clearly define the roles and responsibilities of different stakeholders as well as to create a platform that enables effective coordination among these stakeholders. The WHO Collaborating Center for International Drug Monitoring in Uppsala, Sweden (WHO/UMC) is a critical stakeholder in this respect and over several decades has provided support to many countries for establishment of pharmacovigilance systems. Many countries are now full or associate members of the international drug monitoring program.

The findings from the assessment show that Rwanda has not formally mapped stakeholders and their roles in pharmacovigilance. Table 3 highlights two examples of the negative effects poor stakeholder coordination can have on pharmacovigilance activities. The assessment identified that initial efforts were made to set up a national pharmacovigilance working committee, but it was apparent that the committee was not functioning optimally and stakeholder coordination was not well spelled out as part of the committee's responsibilities. In addition to the lack of mapping, the lack of stakeholder coordination was clearly visible; several pharmacovigilance-related activities were going on without the knowledge of key figures within the ministry. Moreover, medicine safety data being generated by the public health programs are not captured and used for decision making at the national level. However, donors and development partners are already sensitized and supportive to the need for a pharmacovigilance system in Rwanda. Besides the Ministry of Health, other bodies such as the U.S. President's Emergency Plan for AIDS Relief, the President's Malaria Initiative, the Global Fund to Fight AIDS, Tuberculosis and Malaria, the U.S. Centers for Disease Control and Prevention, the U.S. Agency for International Development, and the WHO are leveraging funding for pharmacovigilance.

**Table 3. Impact of Lack of Stakeholder Coordination**

<b>Constraints</b>	<b>Impact</b>
Pharmacovigilance activities are isolated and uncoordinated.	Inefficient use of resources
Public health programs do not consistently track and consolidate ADR and treatment failure data.	No data to inform decisions on treatment guidelines

As these various streams of funding and actions move forward, maintaining effective coordination to achieve results that are complementary and synergistic will be important. It is recommended that a comprehensive mapping document be developed to describe pharmacovigilance stakeholders and their roles and responsibilities. This process will help

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<sup>11</sup> Pirmohammed, M., K. N. Atuah, A. N. O. Dodoo, and P. Winstanley. 2007. Pharmacovigilance in developing countries. *British Medical Journal* 335:462.

identify gaps, plan and improve coordination, and advance efforts on pharmacovigilance and medicine safety monitoring.

### **Signal Generation and Data Management**

The pharmacovigilance process involves signal detection, hypothesis testing and risk quantification, and risk management.<sup>12,13</sup> Reporting of suspected adverse events is therefore the first step in a comprehensive pharmacovigilance process. When adverse events that are suspected to be related to health products used in the country are reported, it helps initiate the process of signal detection. A rigorous data management system is usually required for adverse event reporting and signal detection. The development of a unified data management system that receives and collates pharmacovigilance data from all sources in a country will help coordinate and maximize data utilization, synthesis, and interpretation as well as comprehensive and effective results dissemination, communication, and response.

The scope of pharmacovigilance has recently broadened from its traditional focus on rare and previously unknown ADRs to include other aspects, such as medication error, drug quality, and therapeutic ineffectiveness. The assessment identified a draft form for reporting suspected ADRs, but this form has no field to capture medication errors, product quality problems, and suspected treatment failures. There are no separate forms to do so either.

Integration of locally relevant and contextualized pharmacovigilance topics in pre- and in-service education is vital to prepare and refresh knowledge and skills of health care providers. Public education on responsible and informed self-medication and attention to medicine safety are equally vital for a comprehensive approach to supporting the medicine safety system. As the pharmacovigilance system starts building up, Rwanda will need to invest in pre- as well as in-service trainings. The constraints and impact of inadequate systems for signal generation and data management are listed in table 4.

The assessment identified that Rwanda recently developed an in-service pharmacovigilance training curriculum. Based on this curriculum, the Ministry of Health conducted the country's first training-of-trainers (TOT) course for health professionals in September 2009 in collaboration with MSH/SPS. These TOT-trained trainers are expected to facilitate and lead future trainings, which will prepare additional cadres of trained professionals and further strengthen in-country training capacity. Additionally, work is under way to revise the pharmacy curriculum of the National University of Rwanda, thus providing the opportunity for inserting pharmacovigilance topics into preservice programs.

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<sup>12</sup> Bisson, G., R. Gross, V. Miller, et al. 2003. Monitoring of Long-Term Toxicities of HIV Treatments: An International Perspective. *AIDS* 17(17).

<sup>13</sup> 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.

**Table 4 Impact of Lack of Adequate Systems for Signal Generation and Data Management**

<b>Constraints</b>	<b>Impact</b>
ADR forms not approved and in use.	<ul style="list-style-type: none"> <li>• Health care workers and consumers cannot report adverse events suspected to be related to the health product they used.</li> </ul>
Draft ADR form does not cover the entire scope of pharmacovigilance.	<ul style="list-style-type: none"> <li>• Opportunities for using the same data collection system to address multiple safety issues are lost.</li> </ul>
No system is in place for collation of ADR data from all sources.	Opportunities are lost for developing comprehensive understanding of safety and effectiveness of products used in Rwanda.
Lack of in-service and preservice training	Health care providers have limited skills to monitor adverse events.

In many countries, signal generation relies on sensitized health care workers and stakeholders who report suspected adverse events. Rwanda should review the ADR form to include fields for monitoring product quality and treatment ineffectiveness. Because Rwanda is in an early phase of putting together a pharmacovigilance system, it has the opportunity to take a comprehensive approach and encompass these elements while developing data generation and management mechanisms. The opportunities provided by the recently initiated national pharmacovigilance training efforts should be fully capitalized on to prepare and empower a cohort of trainers that will drive pharmacovigilance activities in Rwanda.

### ***Risk Assessment and Evaluation***

When signals are generated from pharmacovigilance activities, it is imperative to assess and evaluate them—particularly signals that have significant public health importance. The periodic review of the number and types of drug-related adverse events through passive surveillance (spontaneous reporting) as well as evaluation of significant safety issues through active surveillance are fundamental attributes of any comprehensive pharmacovigilance and medicine safety system. Active approaches to surveillance are particularly valuable for public health programs such as HIV/AIDS, TB, and malaria programs and can provide useful information for decisions involving revision of treatment guidelines.

The findings from the assessment indicate that Rwanda has yet to implement most of these risk assessment and evaluation activities. However, some discrete and isolated good practices are in place in some health facilities and programs. Notably, the HIV/AIDS Program is already using a pharmacy ART register that collects ADR data longitudinally (attached as annex 1). This practice provides a major opportunity for the routine collection of ADR data in the ART program. It can serve as a great resource for quickly collecting and analyzing data on the tolerability of antiretroviral medicines and can serve as a precursor for the establishment of sentinel surveillance sites for ART toxicity monitoring. During the assessment, the Ruhengeri hospital was able to quickly provide data on ADRs experienced in the ART program by reviewing the pharmacy ADR register of the ART program. The data showed 50 cases of side effects: 19 cases of lipodystrophy, 15 neuropathies, 7 cases of skin rash, 5 cases of central

nervous system toxicity, 2 cases of anemia, and 2 cases of digestive disorders. Unfortunately, however, this sort of collection is not routinely done at the health-facility level or at the national level. Therefore, the data have neither been systematically collated and analyzed nor used for taking any action. Because opportunities exist for routine collection of ADR data, the HIV/AIDS Program has the potential to make significant progress in ART risk management by moving to the second step of analyzing and using the available data.

Also of note in Rwanda is that the PNILP is supporting active surveillance study for exposure to artemisinin-based combination therapy (ACT) during pregnancy. The assessment found that this study is at its preliminary stages, and efforts are needed to strengthen its protocol, sample size, and implementation. In addition, a drug quality study for ACT is currently being conducted in collaboration with the University of Liverpool. Furthermore, the CHW program has outlined plans for establishing active monitoring of ACT. The patient card used in the program (*Fiche individuelle de prise en charge de l'enfant malade par l'ASC*) contains fields that can be used for determining exposure to ACT and treatment outcome, which are the key data required in all studies for monitoring toxicity-related treatment outcomes. In annex 2, relevant parts of the form have been attached and those fields have been highlighted. The assessment was also informed of previous studies that had reviewed the safety and effectiveness of sulfadoxine-pyrimethamine use in intermittent preventive treatment for the prevention of malaria in pregnancy. This study was credited with having contributed to the decision to suspend intermittent preventive treatment program in Rwanda. The ongoing active surveillance activities identified during the assessment are listed in table 5. These public health program-based active approaches to assessing risk will significantly contribute to improving the medicine safety situation at the population level.

**Table 5. Ongoing Efforts in Active Surveillance**

<b>Activity</b>	<b>Objectives</b>
Pharmacy ADR register for the ART program	To collect longitudinal data on significant ADRs experienced by patients receiving antiretroviral medicines
ACT exposure in pregnancy	To study the outcomes of inadvertent ACT exposure during pregnancy
Drug quality study for ACT	To study the quality of ACTs procured and in use for the management of malaria in Rwanda
CHW presumptive management of malaria program	To routinely collect data for the study of safety of ACT use in the CHW program (the modalities for the study are still being discussed)

This analysis recommends that the ongoing efforts at actively monitoring the safety and quality of public health programs should be strengthened through review of protocols, inclusion of more sites and increased sample size, involvement of more stakeholders, and increased funding to ensure that the studies are rigorous and their findings can provide an evidence base for treatment guideline changes and management decisions. It is also recommended that systems be developed

immediately for how to evaluate signals of public health importance that are generated. Such systems should be well described in the national guidelines and fully implemented.

### ***Risk Management and Communication***

To effectively manage risks, pharmacovigilance systems need to use approaches that actively look for what medicine safety risks exist and what the degree of these risks are. Global stakeholders working on pharmacovigilance increasingly emphasize the need to improve safe use of medicines.<sup>14,15</sup> Increasing emphasis is being laid on “preventing or minimizing risk” rather than focusing on identifying, analyzing, and managing harm after it has already occurred. Examples are (a) putting in place SOPs in facilities to prevent medication errors, (b) strategies to reduce the incidence of harm from high-risk medicines such as heparin, and (c) use of prequalification schemes (such as the WHO prequalification program) for procurement to reduce the risk of buying poor-quality medicines. If effectively implemented, such preventive approaches have a significant potential to reduce the incidences of harm caused by medication use. The U.S. Food and Drug Administration is also strongly emphasizing risk management through recent programs such as the risk evaluation and mitigation strategies.<sup>16</sup>

During the assessment, the PTF was found to have taken local actions in the past relating to pharmacovigilance based on six WHO drug alerts (e.g., Viracept). Additionally, drug and therapeutics committees are growing in number in health facilities in Rwanda, and several of them are already addressing issues related to pharmacovigilance. The draft national pharmacovigilance guideline identifies drug and therapeutics committees as “decentralized units” for NPMIC, thereby recognizing and expecting these bodies to play a key role in the overall conduct of pharmacovigilance in Rwanda. Encouragingly, during the assessment it was noted that some facilities in Rwanda have forms of risk mitigation strategies for high-alert medicines. Although some of these strategies are not formalized and developed as protocols, respondents were consistent in the way they described how they function. The risk management and communication activities identified during the assessment are listed in table 6.

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<sup>14</sup> U.S. Food and Drug Administration. FDA Safe Use Initiative: Collaborating to Reduce Preventable Harm from Medications. <http://www.fda.gov/Drugs/DrugSafety/ucm187806.htm>.

<sup>15</sup> 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.

<sup>16</sup> U.S. Food and Drug Administration. Guidance for Industry Format and Content of Proposed Risk Evaluation and Mitigation Strategies (REMS), REMS Assessments, and Proposed REMS Modifications. <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM184128.pdf>.

**Table 6. Risk Management and Communication Practices in Place**

<b>Risk Event</b>	<b>Risk Management Initiative Undertaken</b>
Alert on the contamination of nelfinavir (Viracept)	Local communication to health facilities and health care workers; recall processes were also initiated.
Safe use activities in health facilities	<ul style="list-style-type: none"><li>• SOPs to prevent error-prone abbreviations are available in one referral hospital.</li><li>• Some restrictions exist for anesthetics and psychotropics.</li><li>• Increased reports of severe headache caused by bupivacaine is being studied in one referral hospital.</li><li>• In another hospital, co-trimoxazole-implicated Stevens-Johnson syndrome reported at a rate of 1.14 percent is being studied.</li><li>• Several cases of suspected substandard products were identified, including discolored aspirin, friable co-trimoxazole, and poor-quality infusion sets, were reported and are being studied.</li></ul>

While building up its pharmacovigilance system, Rwanda should give strong attention to plans and strategies that prevent or minimize risk. These represent some of the most relevant priority interventions that resource-constrained countries can implement to support pharmacovigilance in their settings. With the establishment of the NPMIC, medicine and pharmacovigilance information activities, including a query-answering service and ADR bulletins, will potentially take off and provide up-to-date and independent information to help stakeholders make informed actions. The public is a major stakeholder, which is often paid inadequate attention. To build a comprehensive pharmacovigilance system, implementing information, education, and communication activities for behavior change communication on medicine safety for the public and community using locally appropriate contexts and social marketing approaches will be important.

### **Overall Recommendations**

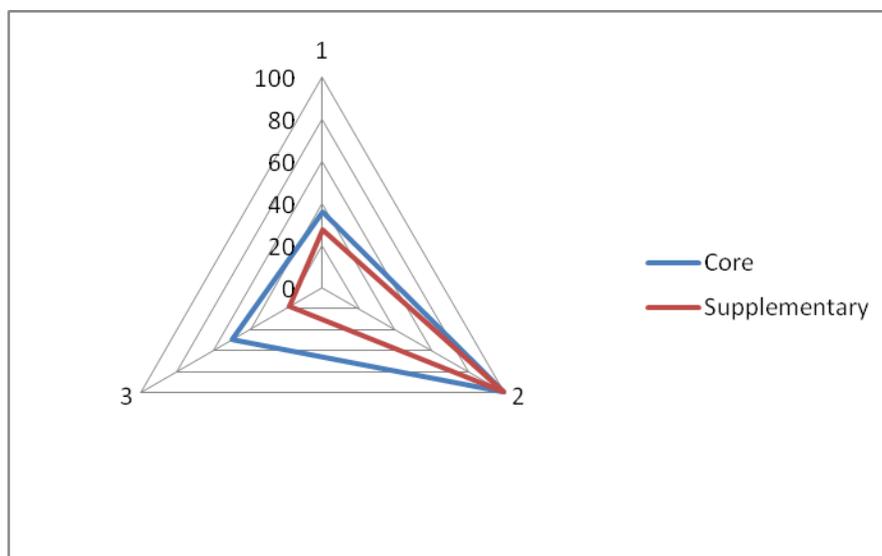
During the presentation of these findings and the recommendations, Rwanda was advised to consider some of the recommendations as requiring priority attention and to put efforts in place to address them. These priority interventions are summarized here.

- Approve the National Medicines Policy and the pharmacovigilance-related aspects of policy documents, and approve the draft Food and Drug Act and other related laws that will allow adequate monitoring of safety of health products.
- Establish the NPMIC as early as possible.
- Approve the draft national guidelines for medicine safety surveillance.

- Prepare an initial core group of in-country experts and trainers by providing them a TOT on pharmacovigilance.
- Establish a multidisciplinary “Medicine Safety Committee” to assist the NPMIC on technical matters.
- Strengthen the national pharmacovigilance working committee to enable it to advance pharmacovigilance and medicine safety activities.
- Strengthen the drug and therapeutics committees to monitor safety and treatment failure.
- Develop a system for tracking suspected treatment failure.
- Support active surveillance—
  - Strengthen ongoing efforts of the PNILP to study the safety of ACT in situations of inadvertent exposure during pregnancy.
  - Implement safety monitoring within the CHW program.
  - Use ADR data from the HIV/AIDS program to inform guideline revision.
- Develop a mapping document to identify all pharmacovigilance stakeholders in Rwanda and identify their current roles and the gaps that exist.
- Initiate a cascade of trainings led by the TOT-trained trainers.
- Work with the National University of Rwanda to adequately address pharmacovigilance topics in the pharmacy curriculum.
- Implement locally suitable strategies to stimulate reporting on drug-related adverse events.
- From early on, emphasize medicine safety by putting in place risk mitigation systems, protocols, and SOPs.
- Coordinate all players and stakeholders to improve efficiency.
- Integrate a monitoring and supervision plan from the beginning.

It was also recommended that a format be developed that will enable pictorial representation of the current status of pharmacovigilance and the medicine safety system. This visualization will assist in recognizing improvements as they occur. A sample of such schematic representation is shown in figure 3, where the responses to the assessment questions and the indicators (disaggregated as core and supplementary) are reduced to Yes/No answers, scored, and presented as a radar chart. For instance, each core indicator with a “Yes” response is scored 2, and each supplementary indicator with a “Yes” response is scored 1. A functional pharmacovigilance and

medicine safety system should answer “Yes” on all 26 core indicators, receiving a score of 52, which is equivalent to 100 percent. For such a system, the blue lines would reach the outer tips of the axes of the chart in figure 3. Likewise, when the 17 supplementary indicators are met, a score of 17 will have the red line at the outermost part of the chart. The blue and red lines in figure 3, show the current situation of the pharmacovigilance system with regard to the core and supplementary indicators, which are substantially less than 100 percent. The IPAT document<sup>17</sup> provides additional information on presenting the assessment findings as a radar chart.



**Figure 3. Sample radar chart of current situation of pharmacovigilance system**

<sup>17</sup> Strengthening Pharmaceutical Systems (SPS) Program. 2009. *Indicator-Based Pharmacovigilance Assessment Tool: Manual for Conducting Assessments in Developing Countries*. Submitted to the U.S. Agency for International Development by the SPS Program. Arlington, VA: Management Sciences for Health.



## CONCLUSION

IPAT was found useful for a comprehensive assessment of the pharmacovigilance and medicine safety system in Rwanda. IPAT can also be used for routine monitoring and evaluation of progress that Rwanda attains in efforts to improve safety of health products used within the country. Rwanda's progress in pharmacovigilance should be built on foundations that already exist, particularly the interest and leadership of the ministry of health in pharmacovigilance, the interest by the public health programs in initiating active surveillance activities, and risk management practices already in place at treatment facilities. Rwanda should introduce pharmacovigilance as creating added value for ongoing initiatives, rather than as a "new" and "competing" initiative. Rwanda should also pay attention not only to developing policies, guidelines, and SOPs but also to implementing and enforcing them. This systems analysis has provided a baseline and recommendations to inform Rwanda's efforts in developing robust systems for the monitoring of the safety of health products used in the country.



# ANNEX 1. PHARMACY ADR REGISTER FOR THE ART PROGRAM

## Rapport des Visites à la Pharmacie

Noms:  
No TRACNET:  
Date de début des ARV:

Allergie:

Date de naissance :  
Sexe:

ARV Régime et Dosage	Date Début	Date Arrêt	Raison(s) d'arrêt**	IO Régime et Dosage	Date Début	Date Arrêt	Raison(s) d'arrêt**										
				Bactrim													
				Dapsone													
				Fluconazole													
				Anti TB													
<b>**Raisons d'interruption des médicaments:</b> 1=Echec 2*TB/excuse/interaction médicamenteuse 3=Effets secondaires/allergie 4=Toxicité (spécifie) 5=Grossesse 6=Rupture de stock 7=Immunité acquise 8=Autre raison:																	
<b>Abréviations des molécules</b> INRI AZT=ZDV=Zidovudine D4T=Stavudine 3TC= Lamivudine ABC= Abacavir TDF= Tenofovir DDJ= Didanosine INNEI, NVP= Nevirapine EFV= Efavirenz IDV= Indinavir LOP/R= Lopinavir/ritonavir NFV= Nelfinavir SQV= Saquinavir R= Ritonavir sp= stop																	
Date de Visite	Visite Respectée	Poids	Eruptions cutanées/Prurit	Nausées/Vomissement	Dyspnée/conjonctivite	Pain de Mal de tête	Paresthésie	Vertiges, cauchemars, insomnie	Troubles psychiatriques	Douleur abdominale	Diarrhée	Jauisse	# de doses manquées dans les 7 jours passés (ARV/Bactrim)	# de comprimés restants (ARV/Bactrim)	Date de Prochaine RDV médicale	Autre médicament	Actions



## ANNEX 2. RELEVANT FIELDS FOR MONITORING SAFETY IN THE CHW MALARIA PROGRAM



**FICHE INDIVIDUELLE DE PRISE EN CHARGE  
DE L'ENFANT MALADE PAR L'ASC**

*Initial visit*

**1. IDENTIFICATION**

District:  Secteur:

Date:  FOSA:  Village:

Nom de l'enfant:  Parent:  ASC:

Date de naissance:  Age:  an(s)  mois  Sexe:  F  M  Début de la maladie:  jours

*Treatment exposure*

**4. SYMPTOMES, CLASSIFICATION, TRAITEMENT & POSOLOGIE**

SYMPTOMES	CLASSIFICATION	TRAITEMENT
Fièvre <input checked="" type="checkbox"/> <input type="checkbox"/>	Fièvre à référer <input checked="" type="checkbox"/> <input type="checkbox"/>	
	Paludisme <input checked="" type="checkbox"/> <input type="checkbox"/>	Coartem <input type="text"/> Tuku <input type="text"/> Hondo <input type="text"/>

*Outcome Follow-up with the health center*

**7. SUIVI DU MALADE**

VISITE DE SUIVI EFFECTUEE:

a. Revenu selon le RDV : après 1jour  3 jours

b. Revenue immédiatement suite à l'aggravation de la santé de l'enfant

c. Visite de suivi à domicile

