



## Rapid Pharmacovigilance Implementation in Developing Countries

### Responsible Scale Up of Treatment Programs Can Save Lives—

### Why Public Health Programs Should Implement the RaPID Approach to Pharmacovigilance

Donor funded public health programs are being scaled up aggressively in order to save lives. However, experience has shown that drugs can also kill if not administered appropriately. According to a study in the US, adverse drug reactions are the 4-6<sup>th</sup> highest cause of death<sup>1</sup>; and similar studies in European countries indicate that 11.5% to 16% of all hospital admissions are caused by adverse reactions to drugs. Unfortunately, such data is not available for most developing countries and there is a growing concern that the long-term use of antiretrovirals, anti-TB drugs and new anti-malarial drugs on such a large scale, could potentially lead to a significant number of adverse drug reactions. The concern is even greater for highly-vulnerable groups like pregnant women and young children—for example, it is feared that “adverse effects associated with antiretroviral medicines ...occur in up to 30% of HIV-infected children on antiretroviral therapy”<sup>2</sup>.

*“Some remedies are worse than the disease”*

*Publilius Syrus, Roman writer, 1st century BC.*



<sup>1</sup> Source: Lazarou et al JAMA 1998;279: 1200 – 1205-

<sup>2</sup> WHO report “Promoting Safety of Medicines in Children, Sep 2007

## **Background on Pharmacovigilance:**

Pharmacovigilance is defined by WHO as **“the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other possible drug-related problems”**

Drug toxicity is a relatively common phenomenon—despite a stringent drug safety and clinical trials process, several drugs have been removed from the market after being approved by National Drug Regulatory Authorities, including US’ FDA, UK’s MHRA, and Europe’s EMEA [refer to annex of drug withdrawals]. In addition to the removal of potentially toxic drugs from the market, one out of every five drugs<sup>3</sup> are required to add additional warnings related to side-effects, contraindications, etc.

Low- and middle-income countries that are rapidly scaling up ART often have relatively little knowledge and/or expertise with regard to pharmacovigilance and simply do not have the resources and manpower to set up vigilance systems for active drug safety and toxicity monitoring like those of their western counterparts. Globally, only about 500,000 to 700,000 adverse event occurrences are captured each year<sup>4</sup>—however, *low- to middle- income countries, which represent more than two-thirds of the world’s population account for a tiny fraction of all the ADR data.*

The concern for ADRs in highly vulnerable populations is of even greater concern. For example, in pediatrics, antiretroviral treatment (ART) intolerance and toxicity is a major cause of poor adherence, changing medications and eventually dropping out of a treatment program. *“Adverse effects associated with antiretroviral medicines have been reported to occur in up to 30% of HIV-infected children on antiretroviral therapy.”* Presently, the non-availability of appropriate pediatric formulations forces many health care providers to resort to administering portions of crushed or dissolved tablets and capsules. As a result children often do not receive the correct dosage—this is all the more dangerous for drugs with a narrow therapeutic window. For these reasons, it is estimated that potentially harmful side effects may be three times more common in children than in adults. Given these risks, stakeholders must ensure that scale-up of ART treatment, especially in the pediatric population, is implemented responsibly, with the appropriate monitoring of patient safety in place. *This is especially important since “most of the adverse effects are reversible by modifying the dosage or omitting the offending medicine.”*<sup>5</sup>

By the end of 2007, an estimated 100,000 children in low- to middle-income countries will have started life-long use of antiretroviral treatment—yet very few countries have an effectively functioning pharmacovigilance system for monitoring the appropriate use and collection of drug safety data.

Establishing new pharmacovigilance programs or strengthening existing ones takes several years and WHO and the Uppsala Monitoring Centre (UMC) have been conducting training seminars for more than 15 years. Despite this effort, UMC estimates that most developing

<sup>3</sup> Lasser KE, Allen PD, Woolhandler SJ, Himmelstein DU, Wolfe SM, Bor DH. Timing of new black box warning and withdrawals for prescription medications. JAMA 2002; 287:2215-20

<sup>4</sup> Uppsala Monitoring Center

<sup>5</sup> The above quote and a lot of the above information is discussed in the new WHO report *“Promoting Safety of Medicines in Children, Sep 2007*

countries (with few exceptions) have limited capacity—and as indicated above, very little adverse drug reaction information is collected, analyzed or formulated into policies for increasing patient safety (e.g. if a drug is causing toxicity, should it be removed as the drug of choice and replaced with another one, or should it be withdrawn from the market altogether?)

### **The RaPID Approach**

**RaPID's mission is to conduct pharmacovigilance on behalf of public health programs and to strengthen national pharmacovigilance capacity in developing countries**

The most significant benefit of the RaPID program is that it can establish a country and disease-specific drug safety program within 90 days, while concurrently helping to build institutional capacity at the country level, which requires several years (>3-5 years). The RaPID program can help National Drug Authorities in capturing ADR data, entering the data into UMC/WHO's Vigiflow software, and having the data analyzed by a team of RaPID Program global experts that have a technical background in HIV/AIDS, TB and malaria, pediatrics, pharmacologists, toxicologists, etc.

It is important to emphasize that all activities of the RaPID program will be coordinated with and jointly developed with the national drug authority, which participates in most of the steps of the process as outlined on the next page.

### **RaPID Program's Technical Organizations and Institutes**

The RaPID Program is being implemented in joint technical collaboration with leading pharmacovigilance institutions from the developed and the developing world including the **Uppsala Monitoring Centre in Sweden**, the national regulatory authority of Switzerland (**Swissmedic**) and other organizations that are providing activity specific expertise activity e.g. **WHO (various departments)**, **Ecumenical Pharmaceutical Network**, **Indian Institute of Health Management Research (a WHO Collaborating Center)**, etc. In addition, we are in discussions with MSF, CHAI, PSI, MIT-Zaragoza, International Federation of Pharmacist, etc.

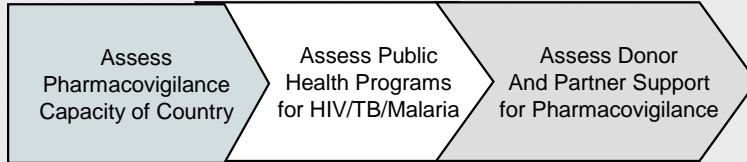
The RaPID program team has significant expertise in designing and implementing pharmacovigilance programs:

### **RaPID's Current Portfolio of Activities**

- With support from WHO/Geneva, the RaPID Program is currently conducting an assessment of a several countries in Africa to gauge their capacity for conducting pharmacovigilance data gathering, data analysis and formulation of appropriate policy related to drug use.
- The RaPID Program team is in discussion with several countries (Nigeria, Sri Lanka, Uganda, India) and NGOs (Medicines Sans Frontier, PSI, etc) to explore collaborations and strategies for conduct pharmacovigilance data entry and data analysis.

## Key activities and roles of partners

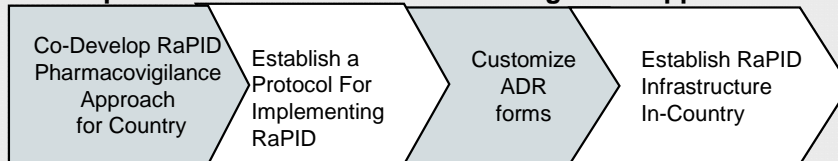
### Analyze Pharmacovigilance Capacity In-Country



### Implementing Org

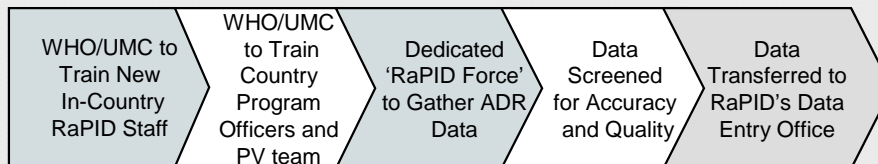
In-country PV Dept, WHO, RaPID team

### Develop a Customized RaPID Pharmacovigilance Approach for Country



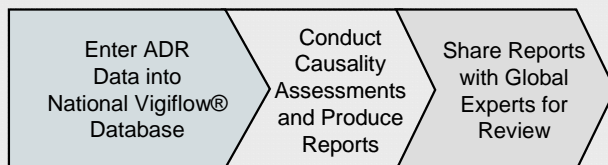
In-country PV Dept, WHO, RaPID team

### Gather Data and Ensure Quality



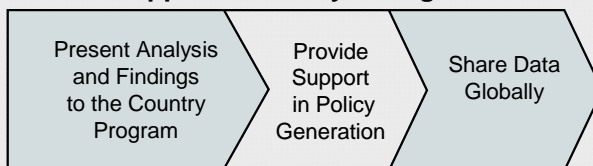
UMC, WHO, Swissmedic, In-country PV Dept, RaPID team

### Analyze Data



RaPID Data entry team, In-country PV Dept, UMC, WHO

### Provide Support for Policy Change



In-country PV Dept, WHO, UMC, Swissmedic, RaPID team

## Illustrative Examples of Services Offered by RaPID Pharmacovigilance Program:

### ***Illustrative Activity:***

Several countries and health programs have already collected valuable data on adverse drug reaction over the past few years but have not analyzed this important information. Most of this data is sitting in dusty boxes or folders and is of little value unless the information is entered into a pharmacovigilance database, checked for quality and consistency, analyzed by experts and eventually converted into policy decisions for implementing public health programs. RaPID can conduct these activities and report the findings back to the public health programs and NDA's of the respective partner countries.

**Partners:** This project would be conducted in collaboration with the Ministry of Health of the partner country, the national public health program, WHO and UMC.

### ***Illustrative Activity:***

By the end of 2007 an estimated 100,000 pediatric patients are expected to have initiated lifelong ART. Given the limited capacity in many of the ART centers, very little drug safety data is being collected and that too, of variable quality. One approach being developed is to deploy the "RaPID Pharmacovigilance Force" staff in about 20% of the sampled sites to collect critical data on adverse events in the pediatric population (for details see box 1 below). This approach provides information on incidence as well as information on serious and unexpected adverse events—i.e. both numerator and denominator information will be captured. With this new information, public health programs can provide better quality of care to pediatric patients.

**Partners:** This project would be conducted in collaboration with Ministry of Health, NDA, WHO country office/ HIV/AIDS office, Program Implementing Organization (e.g. MSF, The Clinton Foundation, etc), and the Uppsala Monitoring Centre.

### ***Illustrative Activity:***

Use of artemisinin combination treatments (ACTs) are being scaled-up through funding from various donors and multilateral banks. Many developing countries are also placing ACTs on their OTC list of products in order to increase access. As access increases, so does risk, as more people start to consume this product. Although it appears to be reasonably safe in adults, its effects in children and pediatric population is still not clear.

**Partners:** This project would be conducted in collaboration with the Ministry of Health/National Malaria Control Program, WHO Global Malaria Program, WHO-in country, Roll Back Malaria Partnership, Uppsala Monitoring Centre.

**Box 1: How the RaPID model works at country level with a pediatric HIV/AIDS program**

The RaPID team first assesses the existing capacity of a national pharmacovigilance program and the scale of the HIV/AIDS pediatric program. The RaPID team coordinates all its activities with a point person in the country's pharmacovigilance program, as well as the head of its pediatric HIV/AIDS program.

After an analysis of the current landscape, a methodology and protocol is established and jointly developed between the RaPID team and the in-country experts. Let us assume that 12-trained RaPID Force (RF) team members (usually nurses or pharmacists recruited locally) will be posted in 12 ART centers. These centers will have been selected based on criteria such as volume of patients, geographic distribution, capacity at the ART centers, etc.

When ADRs (adverse drug reactions) are discovered, the RaPID Force team will collect the information on special ADR forms that have been modified to include components of the national ADR form (if one exists) and also with additional fields related to data to be captured for children and HIV/AIDS.

The RF staff in the 12 centers dispatch their ADR forms (hard copy) to the central RaPID office daily or weekly (depending on the number of reports) where the data is inspected for quality (completeness, timeliness, etc). The RaPID office in the country then scans and uploads the ADR form onto the RaPID website [[www.rapidpharmacovigilance.org](http://www.rapidpharmacovigilance.org)]. In India, a team of pharmacists and doctors download the ADR form and enter the data into WHO/UMC's Vigiflow® software, which has been jointly developed by Swissmedic, the Swiss NDRA. These experts take about 30 minutes to 1 hour to complete the entry of each form into Vigiflow.

The data is then presented in various formats and every week it is sent to a team of global experts—in the case of this example, this would include experts in HIV/AIDS, pediatrics, toxicology, pharmacology, etc. The experts respond within a week, using a common template to ensure consistency in outputs. These responses are aggregated and reported back to the RaPID office in the country and then shared with the national pharmacovigilance center and the national pediatric HIV/AIDS health program. The public health programs use this information to titrate their program to increase effectiveness and improve outcome.

Finally, with the permission of the NDRA, the data is reported to WHO/UMC for inclusion in the global database, providing a global public good for other countries too.

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With this approach, the RaPID Pharmacovigilance Program can establish the pharmacovigilance program in most countries and settings within 90 days and then provide continuous assessments and feedback on the collected ADR forms.

**RaPID Pharmacovigilance Program for Antimalarials:** The approach for collecting data on antimalarials requires a different approach as the care and treatment follows a 'dispersed' model and is not conducted in specified ART-type centers. One of the approaches that has shown some promise is the 'Cohort Event Monitoring' approach, where 10,000 to 30,000 patients are identified before they take the medication, and then are followed closely for the next 21 days to determine the occurrence of ADRs. This model requires significant resources, but is normally time-limited.

***“They poured drugs of which they knew little into bodies of which they knew less”***  
*Voltaire (1700AD)*

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