

Access to New Health Products in Low Income Countries and the Challenge of Pharmacovigilance

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Paul Lalvani and Julie Milstein¹

Abstract

The authors conducted an assessment of pharmacovigilance (PV) strategies on behalf of the Product Development Partnership (PDP) Access Steering Group. The assessment was based on interviews with 13 PDPs, 13 regulatory authorities (NRAs), and 7 technical and stakeholder agencies.

This assessment applies the broader definition of PV which includes activities related to safety monitoring of therapeutics and vaccines during clinical development and post-product launch—a complete life cycle approach. In order to assess the safety of products during all stages, NRAs require Development Risk Management Plans (DRMPs) as part of the Clinical Development Plans at the outset of clinical trials (CTs), and these evolve to Risk Management Plans (RMPs). As the product moves from the early development stage to clinical development and finally to the market, the knowledge regarding the safety profile of the product also increases proportionately.

Once the product is marketed, PV covers a range of activities including passive surveillance, stimulated reporting, active surveillance, comparative observational studies and targeted clinical trials. In several developing countries with rudimentary or emerging PV capacity, mostly passive surveillance systems exist. Developed countries use a mix of PV strategies to ensure the drugs and vaccines have a favorable benefit-risk profile.

Most PDPs have PV capacity during CTs, although the extent of their involvement in PV activities varies depending on the phase of development of the product and the entity conducting product development (i.e. the PDP or a commercial partner). These PV activities during CTs are important for setting the stage for post-marketing surveillance (PMS) and for exploring the possibility of building PV capacity in countries targeted for product introduction.

PMS largely depends on the strength and capacity of the overseeing NRA to guide and enforce PV activities—the tendency for PDP manufacturing partners is to do less if this activity is not mandated. Activities for PMS are just beginning, except in those PDPs which have products progressing to Phase 3 or are already authorized. These PDPs are developing multiple strategies to address product safety concerns, such as planning and implementing phase 4 studies, sentinel and cohort event monitoring studies.

Some PDPs are thinking about PV more broadly, and in addition to building the capacity of their own staff, these PDPs are planning/helping to build the capacity of PV for NRAs in countries where products will be marketed.

Those PDPs with products earlier in the pipeline have generally not given much consideration to PMS, and are not yet poised to move to the next step; in fact, many felt that PMS strategies were the sole responsibility of the MAH. Even if PDPs are prepared to embark on PMS, funding for these activities is limited.

¹ Prepared by Paul Lalvani (Empower School of Health) and Julie Milstein (consultant) on behalf of the PDP Access Steering Committee, which is made up of the following organizations: Aeras, Concept, DNDi, FIND, IAVI, iOWH, IPM, IVAC, , IVCC, MMV, MVI, PDVI, and TB Alliance

To improve PDP performance in PV and to gain synergies, some specific actions are recommended, including: clearer definition of roles and responsibilities of PDPs throughout the PV life cycle; provision of a handbook which outlines PV regulatory capacities of target countries; tabulation of basic biological markers in specific developing country populations to facilitate evaluation of adverse events; exploration of strategies for centralized sharing among PDPs, such as electronic reporting, capacity building, and trial sites.

Table of Contents

Abstract	1
Chapter 1: Background on equitable access to medicines and relationship of pharmacovigilance (PV) to access	5
1.1 What is access and why it is important?	5
1.2 What is PV and why it is important?	5
1.3 Access and its relationship to PV	6
Chapter 2: Overview of PV strategies	7
2.1 Commonly used PV approaches	7
2.2 Unique Elements of PV in Vaccines	9
2.3 PV strategies in developing and developed countries	10
2.4 PV strategies from a pharmaceutical/vaccine producers point of view	10
Chapter 3: International technical agencies working in PV	12
3.1 World Health Organization (WHO)	12
3.2 WHO-Uppsala Monitoring Centre (UMC) Post-marketing Surveillance (PMS) Network	12
3.3 Council for International Organizations of Medical Sciences (CIOMS)	13
3.4 International Conference on Harmonization (ICH)	13
3.5 Brighton Collaboration	14
3.6 International Society of Pharmacovigilance (ISoP)	14
Chapter 4: PV in developing countries	15
4.1 Assessment of Requirement 1:	15
4.2 Assessment of Requirement 2:	16
4.3 Assessment of Requirement 3:	16
4.4 Assessment of Requirement 4:	16
4.5 Assessment of Requirement 5:	16
Chapter 5: Assessment of PV activities in PDPs	17
5.1 General background of PDP products	17
5.2 State of PV in PDPs	18
5.3 Assessment of type of PV activities being planned	22
5.4 PV and Regulatory Authorities	23
5.5 HR Capacity for PV in PDPs	24
5.6 PV Capacity in countries and the role of PDPs	25
Chapter 6: Analysis of challenges and suggested approaches	26
6.1 Major challenges in conducting PV	26
6.1.1 PDPs	26
6.1.2 Sponsors/MAH/Pharmaceutical or Vaccine Manufacturer	26
6.1.3 National Regulatory Authorities—SRA and non-SRA	26

6.2 Solutions	26
Chapter 7: Concluding Remarks	28
Appendix 1: People interviewed	29
Appendix 2: Scope of work.....	31
Appendix 3: Definitions and terminologies in pharmacovigilance	33
Appendix: 4 Pharmacovigilance Methods.....	34

Chapter 1: Background on equitable access to medicines and relationship of pharmacovigilance (PV) to access

1.1 What is access and why it is important?

The developing world harbors an estimated 80% of the world population's and 90% of the global disease burden, yet accounts for only about 10% of the global pharmaceutical market. In terms of the pharmaceutical R&D budget, the percent amount spent on drugs and vaccines for diseases of the developing world is even less.

This is not surprising, since very few products that target 'neglected diseases' would be profitable, or as profitable as drugs targeting the developed markets. To address this gap, not-for-profit Product Development Partnerships (PDPs) have been established with the mission of developing health products for markets that are neglected by traditional 'for-profit' R&D companies.

The focus of PDPs is not simply to develop these products, but also to ensure availability, affordability, acceptability (or adoption) and rational use of the products — in other words, ensure **access** to these products.

Acceptability has several components and includes inclusion in donors' lists, WHO's standard treatment guidelines, national treatment guidelines, national immunization programs, essential medicines list, and WHO vaccine position papers, as well as acceptance by prescribers, dispensers, health care professionals and consumers, and by donors.

1.2 What is PV and why it is important?

WHO defines PV as the 'The science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug [vaccine]-related problems'². In addition to drugs and vaccines, its concerns have been widened to include herbals, traditional and complementary medicines, blood products, other biologicals besides vaccines, medical devices, and some diagnostics.

Pharmacovigilance is undertaken both during the preclinical and clinical development of a drug and also after the drug/vaccine manufacturer is granted an authorization to produce and market the product commercially.

During pre-clinical development, animal experiments have limited value in predicting human safety. Even human clinical trials are only a partial predictor of product safety—several drugs and vaccines have been authorized for marketing and subsequently recalled due to serious adverse reactions or even death. There are several reasons why clinical trials have limitations in predicting safety:

They are performed on a limited number of patients (100s to 1000s), whereas once the product is launched, it is used by millions, e.g. Artemisinin-based Combination Therapies (ACTs) have been consumed by more than 200 million people. So adverse events that are considered rare (less than 1: 1000), may not occur during clinical trials, but could have major negative consequences once the product is launched.³ Clinical trials patients are selected carefully to exclude the factors that could possibly confound the safety and efficacy measures of the product under study. These are not representative of a 'real life' situation where the patient may have various other pre-existing diseases and conditions and so therefore may be prescribed several other drugs, all of which could be confounders. Therefore, the complete safety profile of a product may not be known at the time of approval of the product for use by the larger population. Different cultures react to drugs differently, and it is just not possible to conduct clinical trials in all the different cultures (genetic make-up, disease patterns, co-morbidities, nutrition status, co-use of herbal and

² The Importance of Pharmacovigilance, WHO 2002

³ Note that since the issues with rotavirus vaccine and intussusception, many vaccine clinical trials have included much larger safety studies, on the order of 50,000-100,000 at phase 3 level. However, even those numbers would not address rare adverse events that occur at a frequency of about 1:1,000,000. If such events are biologically plausible, these are generally addressed in phase 4 trials.

indigenous products, common adverse reactions to drugs in some populations, e.g. Guillain-Barré Syndrome or Stevens-Johnson syndrome in Africa, etc.)

The safety profile of the drug/vaccine is dynamic—as more information is collected, the use of the product may be expanded (new indications, new populations), or become more limited (e.g. not to be used by pregnant women, etc).

For these reasons, it is essential to continue monitoring the safety profile of the product after it has been granted authorization. This ongoing assessment of the risk-benefit profile of the product is referred to as post-marketing surveillance (PMS).

1.3 Access and its relationship to PV

As defined above, access is defined as availability, affordability, acceptability and rational use—***the element of access that is directly linked to PV is acceptability***. For a product to be adopted and used, it must be considered ***acceptable*** to:

- The government, or Ministry of Health of the country (e.g. included in national standard treatment guidelines, essential medicines list), or national immunization schedule)
- Donors, insurance or third party payers (e.g. on their 'positive' list)
- International technical agencies (e.g. WHO's prequalified lists for drugs and vaccines, WHOPES for pesticides)
- Health care practitioners
- Consumers

For a product to be considered acceptable, safety must be demonstrated—some countries, both in the industrialized and the developing world, require the sponsor to develop a plan for PMS. In addition, in the case of drugs, WHO normally requires a PV study before it will 'prequalify' a product—this has a direct impact on affordability (and therefore access) since several donors fund only WHO prequalified products⁴. For vaccines, products cannot be prequalified unless they are under the active regulatory oversight of a functional national regulatory authority (NRA); such an agency is likely to require a PV study as well.

It is apparent from the above discussion that PV and access are directly linked, and the access team of PDPs must be actively engaged in ensuring the conduct of PV—starting with the development phase and continuing well after the product is launched.

⁴ Donors may fund products that are registered with Stringent Regulatory Authorities (SRAs), who also require PMS studies before approving a product.

Chapter 2: Overview of PV strategies

Traditionally, PV has been defined as an activity that takes place after a product is approved for marketing and actually enters the marketplace. However, in the recent past, the trend, mostly driven by ICH and CIOMS⁵ is to apply principles of PV throughout the product life cycle, beginning with the earliest phases of development. Thus in response to ICH E2E and CIOMS VI, major regulatory authorities, such as the European Medical Agency (EMA) and the US Food and Drug Administration (FDA), are defining PV planning in the approval phases of medicines development⁶.

Regulatory agencies focus on safety aspects during clinical development of any product. The various approaches used pre-licensure are laid out in Clinical Development Plans – where the risk considerations and planned steps to deal with them are presented early in the development stage of a product. A specific component of this plan, the DRMP, includes early documentation of known, anticipated or potential risks along with plans for addressing them during development. The DRMP is a vital part of PV and eventually evolves into a post-marketing Risk Management Plan (RMP) thus linking the pre- and post- licensure phases.

2.1 Commonly used PV approaches

There are various methodologies and approaches to PMS. WHO's Pharmacovigilance Toolkit⁷ (for drugs) lists the various approaches and discusses how and when they should be used.

Passive surveillance includes spontaneous reports and case series. Passive surveillance reports (as opposed to active surveillance reports) are unsolicited, and this adds significant value in terms of signal detection, as these are seen as emerging spontaneously from the reporter and thus the causality assigned by the reporter would be more accurately reflective of the clinician's interpretation and judgment.

Stimulated reporting includes several methods used to encourage and facilitate reporting by health professionals in specific situations (e.g., in-hospital settings) for new products or for limited time periods. Such methods include on-line reporting of adverse events and systematic stimulation of reporting of adverse events based on a pre-designed case definition. Although these methods have been shown to improve reporting, they are not devoid of the limitations of spontaneous reporting, especially selective reporting and incomplete information.

Active surveillance includes sentinel sites, drug event monitoring (and cohort event monitoring (CEM)), registries. Active surveillance, in contrast to spontaneous reporting, seeks to ascertain completely the number of adverse events via a continuous pre-organized process. An example of active surveillance is the follow-up of patients treated with a particular drug as in CEM. Patients who fill a prescription for this drug may be asked to complete a brief survey form and give permission for later contact. In general, it is more feasible to get comprehensive data on individual adverse event reports through an active surveillance system than through a spontaneous reporting system.

Comparative observational studies use traditional epidemiologic methods, which are a key component in the evaluation of adverse events. There are a number of observational study designs that are useful in validating signals from spontaneous reports or case series. Major types of these designs are cross-sectional studies, case-control studies, phase 4 and cohort studies (both retrospective and prospective) and demonstration studies.

Targeted clinical investigations are used to evaluate the mechanism of action for the adverse reaction when significant risks are identified from pre-approval clinical trials. In some instances, pharmacodynamic and pharmacokinetic studies might be conducted to determine whether a particular dosing instruction can put patients at an increased risk of adverse events. Genetic testing can also provide clues about which group of

⁵ PPD. Safety Trends in Drug Regulation and their Implication, <http://www.ppd.com>

⁶ Hartford CG, Petchel KS, McKail H, Perez-Gutthann S, McHale M, Grana JM, Marquez P. Pharmacovigilance during the pre-approval phases: an evolving pharmaceutical industry model in response to ICH E2 E, CIOMS VI, FDA and EMEA/CHMP risk-management guidelines. *Drug Saf* 29 (8): 657-673, 2006.

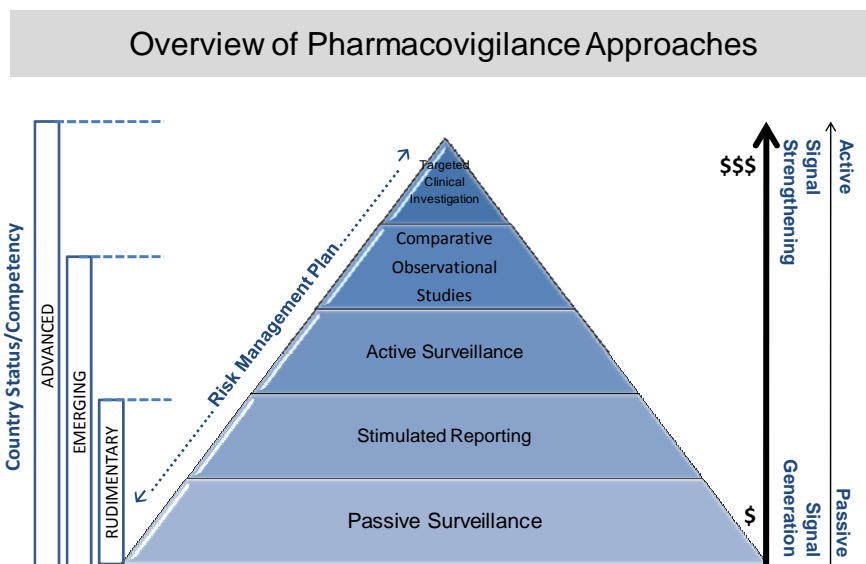
⁷ www. <http://www.pvafrica.org/toolkit/index.html>; the tool kit presents the approaches in a word format; the authors, with support from Dr Vivek Ahuja, a Key Opinion Leader in Pharmacovigilance in India, have formulated the approaches into an illustration.

patients might be at an increased risk of adverse reactions. Furthermore, based on the pharmacological properties and the expected use of the drug in general practice, conducting specific studies to investigate potential drug-drug interactions and food-drug interactions might be called for. These studies can include population pharmacokinetic studies and drug concentration monitoring in patients and normal volunteers.

Some or all of these approaches are often included into a comprehensive RMP developed by the MAH as part of the dossier in order to identify and strengthen signals that may have been generated during clinical trials or during any point in time during the launch of the product.

Each of the above approaches is described in more detail in appendix 4 and has been organized into an illustrative framework by the authors, as presented below:

Figure 1: Overview of PV Approaches



Framework developed by Paul Lalvani, Julie Milstien, Vivek Ahuja (based on WHO's and Global Fund's Pharmacovigilance Toolkit)

Some key points that can be generalized from the framework:

- The approaches at the bottom of the pyramid are mostly 'spontaneous and passive' in nature, whereas the top of the pyramid includes approaches that are 'targeted and active'.
- The approaches at the bottom of the pyramid cost the sponsors less to implement (several thousand dollars), whereas the approaches at the top of the pyramid cost more (several million dollars)
- The approaches at the bottom of the pyramid are focused more on generating signals (providing a suspicion that a particular product, drug or vaccine, may have caused the adverse event (adverse drug reaction - ADR) or adverse event following immunization (AEFI)), whereas the approaches at the top of the pyramid are focused on strengthening signals (i.e. confirming causality)
- The approaches at the bottom of the pyramid are implemented by most countries, and require fewer specialized resources, whereas the approaches at the top of the pyramid are normally implemented by countries with a more advanced PV capacity

It is important to note that countries which use the 'upper parts' of the pyramid still use the 'lower parts' as a basis for signaling.

The conduct of these PV activities is a joint effort between several key-stakeholders, as outlined in the table below:

Table 1: PV activities and Roles of Stakeholders

Roles and Responsibilities		
<i>PV Activities</i>	<i>NRA, Public Health</i>	<i>MAH/Sponsor/development partner</i>
Passive surveillance	Conduct analysis of the data submitted by MAH and health care providers (signal detection, signal strengthening), NRA, Communicate with health care providers/consumers Issue directives (drug withdrawal, limit use, issue warnings)	Aggregate and submit ADR (individual case safety report - ICSR) on a timely basis
Stimulated reporting, active surveillance, comparative observational studies, targeted clinical studies	May mandate, recommend or conduct these activities themselves	Fund and conduct these activities and report to NRA

Passive surveillance is a relatively inexpensive strategy for collecting ADR data from reporters, be they patients or health care professionals. It is not resource intensive, and has reasonably good value for signal detection – provided the data quality is good and the reports are complete and accurate. For these very reasons it is a preferred form of ADR data collection in developing countries. In developed countries, pharmaceutical companies are obliged to conduct PMS activities. In addition to passive surveillance, these could be targeted studies with high scientific focus on a particular safety aspect or could even take the form of registries to focus on particular aspects like pregnancy exposure to drugs. Since these involve a higher commitment, greater technical expertise and financial resources, these activities are more common in the developed world. PDPs bridge the two worlds—they are registering their products in developed countries with SRAs, while preparing to launch their product in developing countries. PDPs will need to establish a RMP that is strategic and thorough while at the same time it should be operational in the developing country environment.

2.2 Unique Elements of PV in Vaccines

Vaccines are normally given to healthy individuals, especially young children, and often on a mandatory basis. In contrast to medicines, they are given to prevent a disease, and so the urgency of receiving them is somewhat lower. Vaccines have a complex composition, a short duration of exposure with a long-term response. The result is that there is lower acceptance of any potential risks. Because of the wide utilization of vaccines, a safety risk could have extensive consequences, and thus rapid evaluation is critical. Also because of their wide-spread use, temporal associations might be seen as causally related, making appropriate causality analysis extremely important.

There are special considerations for PV of vaccines,⁸ which include careful attention to manufacturing methods (including use of adjuvants, stabilizers, preservatives, and residual material from the manufacturing process), batch-related adverse reactions, special attention to target groups and group-specific host factors, to the potential transmission of infectious agents, especially in live attenuated vaccines, and to vaccination schedules and route of administration (because of potential concomitant organisms that might produce an augmented effect). Expedited reporting of cases of lack of efficacy, the non-applicability of causality assessments as applied to medicines, and the potential for programmatic errors complicate reporting of intrinsic adverse reactions.

The RMP pre-licensure will typically deal with such issues as the risk of shedding the vaccine active ingredient, e.g. an attenuated live virus, during the trial, reversion to virulence, and potential for transmission of the vaccine product to close contacts including pregnant women. Also important to consider are concomitant drugs and vaccines, and the possibility of interference in response by other infectious agents.

⁸ Committee for Medicinal Products for Human Use. Guideline on the Conduct of Pharmacovigilance for Vaccines for Pre- and Post-Exposure Prophylaxis against Infectious Diseases. EMEA/CHMP/PhVWP/503449/2007, 22 July 2009.

Vaccine clinical trials, like those for medicines, normally proceed in four phases, the first three of which occur prior to marketing approval. These trials proceed from a small number of individuals for the first in human safety studies (phase 1), to a larger number, perhaps 50-500, but possibly more, for initial determination of efficacy and larger safety studies, to potentially very large (up to 50,000-100,000 individuals) phase 3 trials. These trials will be very important in defining the potential reactions to be studied post-marketing and the PV plan.

Often potential risks seen in clinical trials will be the subject of special studies conducted post-marketing (Post-authorization safety study, PASS, in Europe, phase 4 studies in the US). These are outlined in the RMP. One of the most important differences between the safety monitoring of drugs and vaccines post-marketing is the need for involvement of the immunization program, or the public health sector, for vaccines, because they are often given on a mandatory or semi-mandatory basis to large segments of the healthy infant population by the public health sector itself.

In the US, post-marketing surveillance for vaccines is done through the Vaccine Adverse Events Reporting System (VAERS), jointly administered by FDA and the Centers for Disease Control and Prevention. This is a passive system which accepts reports from physicians, other health care providers, and the public. Manufacturers are required to report to VAERS. Data and potential signals as well as patterns of vaccine distribution data by lot (to provide denominator information) are analyzed by FDA. Potential signals can be validated or discarded through the use of special studies overseen by the NRA using linked databases that can provide almost real time data on actual populations, generally those covered by insurance plans. Some of these can aggregate data on as many as 60M individuals, allowing a quantification of extremely rare risks.

2.3 PV strategies in developing and developed countries

Countries are in different stages of evolution with regards to their PV strategies, which is mostly due to availability of human, technical and financial resources. In Chapter 4, the authors discuss in detail the activities and capacity of developing countries to conduct PV.

Generally speaking, developing countries are focused at the 'bottom of the pyramid', whereas the developed countries work across the entire pyramid—proactively and preemptively.

The PV activities in the developing world are more focused on setting up basic systems to collect data, and to enforce regulations. These activities have been described as 'pharmacodiligence,' reflecting the due diligence aspect of collecting data, whereas the strategy in the developed world is evolving towards risk management and prevention of adverse events. For example, the US and Europe oversee PV throughout the life cycle, starting as early as possible in the clinical process with the filing of PV plans, which, as updated, would become part of the license application, along with risk management or risk minimization plans that would address any adverse reactions uncovered during the clinical trials. These reactions would be the subject of intensive post-marketing studies, if the product were to proceed to marketing.

Canada is moving towards a system similar to that used in the US, except that some of the provinces have mandatory public sector reporting for vaccine reactions. In the case of vaccines, as in many countries, there is an additional signal detection system to specifically pick up vaccine reactions when vaccines are delivered primarily through the public health system.

Refer to chapter 4 for a detailed discussion of the PV capacity of NRAs in developing countries.

2.4 PV strategies from a pharmaceutical/vaccine producers point of view

All regulations governing PV are aimed towards assigning accountability to 'product license holders' (PLH) or 'Marketing Authorization Holders' (MAH). Pharmaceutical and vaccine producers (and in some cases PDPs) are classified as MAH or PLH from a PV regulation point of view. The principle is simple – the product promoter must also be accountable for ensuring public safety.

The primary driver for conducting PV activities is the fear of potential loss of sales in the event the product is withdrawn or if the organization is fined. In developing countries, this risk is practically non-existent due to weak regulations and poor enforcement. Only companies that have a multinational presence, including a

presence in developing and developed countries, tend to be compliant with PV activities. However, even these countries appear to have a 'split personality'—being highly compliant in developed countries while displaying minimal interest in developing countries.

Generic companies are expected to follow the same set of standards as innovator companies for PV. Typically, the budget for generic companies is a small fraction of the budget compared to innovator companies—the annual PV budget for global pharmaceutical MNCs may range from \$5 million to \$20 million while the PV budget for generic MNCs (e.g. Ranbaxy, Cipla, etc.), may range from \$10,000 to \$100,000. Several NRAs, both in the developed and developing world, have allocated significant liability to companies if they do not fulfill the requisite obligations.

Chapter 3: International technical agencies working in PV

There are a number of technical agencies working in the area of PV on the international level. This section outlines the activities of a few of them.

3.1 World Health Organization (WHO)

WHO, both at the global and at the regional levels, has a number of activities in PV in the areas of medicines and vaccines.⁹ The major activities are outlined below.

- Developing and publishing norms and standards with inputs from countries and manufacturers through medicines and biologics Expert Committees
- Activities to strengthen country initiatives in PV and safety monitoring¹⁰: The capacity of immunization programs to detect, investigate, analyze and resolve issues of AEFI, which could damage the credibility of the immunization program, is being strengthened. WHO's Department of Immunization, Vaccines and Biologicals (IVB) is currently leading the Global Vaccine Safety Blueprint Project,¹¹ a study of current performance of vaccine PV systems in low- and middle-income countries, to develop an approach to assist all countries to reach a minimum capacity level in this area. WHO is also working on the Global Network for Post-Marketing Surveillance of Newly Prequalified Vaccines (refer to the box below).

3.2 WHO-Uppsala Monitoring Centre (UMC) Post-marketing Surveillance (PMS) Network

This consists of 12 countries¹² selected based on certain performance criteria representing all six WHO regions. The network's purpose is to provide WHO with PMS data for newly prequalified vaccines, and to build capacity with harmonized methodologies and exchange of PV data among its members. Discussions on the network started over three years ago and reporting started about eight months ago. There have been four meetings to date.

The assessment of PMS characteristics for all 12 countries indicated areas that needed strengthening. For example, one aim is to harmonize data submissions to the global database, using the VigiFlow software data management tool developed by UMC for low and middle income countries. One of the difficulties in forming the network has been to get all necessary permissions and government authorizations for data sharing. There is a large variation in reporting: one country sent more than 2000 cases and another 30.

One of the serious problems with the network is to get regulators in the national PV center and immunization program staff to work together and share AEFI reports. In general, most reports are generated in the immunization program/public health sector, however, regulators mostly receive AEFIs from the private sector (reports by manufacturers). Thus regulators do not get all the AEFI/PMS data they need to perform their task. Another issue is that in many immunization programs, AEFI mainly detect programmatic errors.

The Global Advisory Committee on Vaccine Safety¹³ is a committee of experts set up 10 years ago to provide WHO with independent advice on vaccine safety issues. Examples of vaccine safety issues for which the GACVS

⁹ http://www.who.int/immunization_safety/aeft/en; http://www.who.int/medicines/areas/quality_safety/safety_efficacy/en/index.html

¹⁰ [http://www.who.int/medicines/areas/quality_safety/safety_efficacy/pharmvigi/en...;](http://www.who.int/medicines/areas/quality_safety/safety_efficacy/pharmvigi/en...)

http://www.who.int/immunization_safety/activities/en/

¹¹ This project is maintained and funded under WHO's Vaccine Safety Team through the Uppsala Monitoring Centre, see List of Interviewees for information

¹² Twelve countries (distributed across all six WHO Regions) have been selected by WHO --Senegal, Uganda, Brazil, Mexico, Iran, Tunisia, Albania, Kazakhstan, Vietnam, China, Sri Lanka and India (one selected state). UPPSALA REPORTS July 2009

¹³ http://www.who.int/immunization_safety/global_committee/en/; Global Advisory Committee on Vaccine Safety (GACVS) and WHO Secretariat. Global safety of vaccines: strengthening systems for monitoring, management, and role of GACVS. Expert Review of Vaccines 8 (6): 705-716, 2009.

has provided opinions include the hypothetical link between measles-mumps-rubella vaccine and autism, and the link between hepatitis B vaccine in France and multiple sclerosis. In both these cases the link was found to be unconvincing, while the benefit/risk for both vaccines was overwhelmingly positive.

The WHO Collaborating Centre for International Drug Monitoring, also referred to as the UMC, in Sweden,¹⁴ coordinates the WHO Programme for International Drug Monitoring; collaborates with member countries in the development and practice of pharmacovigilance; identifies and analyses new adverse reaction signals from the case report information submitted to its global database (104 Official Member Countries and 30 Associate Members); provides tools for the management of clinical information such as the WHO Drug Dictionary and the WHO Adverse Reaction Terminology (WHOART); licenses computer software for case report management (VigiFlow) available to the National Centres; and conducts methodological research on PV. Through funding from the Bill & Melinda Gates Foundation, WHO IVB is supporting one vaccine focal point at UMC, Dr Jerry Labadie, who coordinates the PMS Network described above. In 2010, UMC established its first office outside Sweden—referred to as UMC-Africa, it is based in Accra, Ghana and is headed by Dr Alex Dodoo.

WHO's prequalification process for vaccines¹⁵ outlines the role of WHO IVB to investigate serious AEFIs occurring with prequalified vaccines supplied by international procurement agencies to national vaccination programs, as well as the role of the manufacturer and the NRA involved in regulatory oversight of the vaccine.

Examples of ongoing WHO PV projects in the area of drugs include¹⁶:

- Malaria: i) 6 country (Cameroon, Ethiopia, Ghana, Kenya, Nigeria, Tanzania) PV project, with active surveillance (CEM) of ACTs in Tanzania and Nigeria; project will conclude in 2011. Funder: EuropeAid. ii) UNITAID: Supports some aspects of WHO's norms and standards work in PV. As an example, UNITAID has funded WHO to develop RMPs for some prequalified medicines (example: Artesunate Amodiaquine (AS-AQ))
- Malaria / TB / HIV: All three diseases are tackled in a consolidated project with 11 partners, led by WHO and UMC; funded by EC (Framework Programme 7), started in September 2009, will conclude early 2014. Project involves 6 countries in Africa and 3 in Europe.¹⁷
- HIV project: Funded by Gates Foundation to and targeting Kenya, Tanzania, Ukraine, Brazil. Project will conclude 2012.
- Chagas: Project is focused on estimating PV needs for treatment of this disease. Funded by the Japanese government, the project is concluding in April 2011.
- PV activities in the above projects include spontaneous reporting, CEM, Phase 4, registries, and several other approaches.

3.3 Council for International Organizations of Medical Sciences (CIOMS)

CIOMS,¹⁸ also based at WHO, was established jointly by WHO and UNESCO in 1949. Its Working Groups have developed outputs in two areas that are directly related to PV. The first relates to clinical trial safety (CIOMS VI and VII) which defines a process for identification, assessment and management of safety issues throughout the product life cycle.¹⁹ The second is a publication from Working Group VIII, "Practical Aspects of Signal Detection in Pharmacovigilance," which provides standard case reporting forms and definitions.

3.4 International Conference on Harmonization (ICH)

ICH was established in 1990 by authorities and industry in the European Union, Japan, and the United States related to harmonization of specific approaches. Six of its guidelines are specific to PV, covering management

¹⁴ <http://www.who-umc.org>

¹⁵ WHO/BS/10.2155, page 24

¹⁶ Comments from Dr Shanthi Pal, Manager, Pharmacovigilance, WHO

¹⁷ http://ec.europa.eu/research/fp7/index_en.cfm

¹⁸ <http://www.cioms.ch>

¹⁹ Tsintis P, La Mache E. CIOMS and ICH initiatives in pharmacovigilance and risk management: overview and implications; Drug Saf 27 (5): 509-517, 2004.

and expedited reporting of individual cases, periodic reporting, and the use of risk management concepts throughout the product life cycle.^{7,20}

3.5 Brighton Collaboration

The Brighton Collaboration²¹ is an international voluntary collaboration. One of its most important outputs is globally accepted and implemented standardized case definitions of AEFI.

3.6 International Society of Pharmacovigilance (ISoP)

ISoP is an international non-profit scientific organization that fosters PV through promoting regular exchange of information and encouraging PV education at all levels.²²

²⁰ Bahri P, Tsintis P. Pharmacovigilance-related topics at the level of the International Conference on Harmonization (ICH). *Pharmacoepidemiol Drug Saf* 14 (6): 377-387, 2005.

²¹ <http://www.brightoncollaboration.org/internet/en/index.htm>

²² <http://www.isoponline.org>

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Chapter 4: PV in developing countries

The authors assessed PV capacity in 13 developing countries as shown in Table 2.

Table 2: Assessment of PV capacity

Assessment	Vaccine Assessment	Drug Assessment
Developing countries	India, Brazil, Thailand	Africa: Rwanda, Nigeria, Uganda, Madagascar, Kenya, Ghana, Tanzania, Uganda, Zanzibar Asia: India, Cambodia
Developed countries	USA, Canada, EU	EU

The mix of countries was chosen based on several factors:

- Stages of PV 'maturity'
- Countries where the PDPs were planning to introduce the products
- A mix of countries from Africa and Asia
- Large and small countries
- Some countries (NRAs) which are involved in oversight of PDP products
- Data from some developed country SRAs have been included as a comparison for the findings from developing countries.

As discussed previously, SRAs are implementing a comprehensive PV strategy, whereas many developing countries are functioning at the rudimentary level of PV operations. To assess the PV capacity of the selected countries, the authors are leveraging the framework that has been developed by WHO and partners, which lists the "**Minimum pharmacovigilance requirements for NRAs**"²³:

*Requirement 1: A **national pharmacovigilance centre** with designated staff (at least one full time), stable basic funding, clear mandates, well defined structures and roles and collaborating with the WHO Programme for International Drug Monitoring.*

*Requirement 2: The existence of a **national spontaneous reporting system** with a national individual case safety report (ICSR) form i.e. an ADR reporting form.*

*Requirement 3: A **national database** or system for collating and managing ADR reports.*

*Requirement 4: A national ADR or pharmacovigilance **advisory committee** able to provide technical assistance on causality assessment, risk assessment, risk management, case investigation and, where necessary, crisis management including crisis communication.*

*Requirement 5: A clear **communication strategy** for routine communication and crises communication.*

4.1 Assessment of Requirement 1:

National PV centers: 8 of 10 PV centers have been established in the past decade, with only Tanzania and Ghana having been established before the year 2000. In comparison, the developed world PV systems have been established since the 60s and 70s.

²³ http://www.who.int/medicines/areas/quality_safety/safety_efficacy/PV_Minimum_Requirements_2010_2.pdf. For vaccines the indicators are slightly different but include many of the same principles: Institutional regulations and guidelines for monitoring PMS; a quality management system for PMS activities; definition of roles and responsibilities for key personnel; a system for regular review of potential safety and efficacy issues related to PMS; capacity for advanced analysis and investigation, and for regulatory action as a result of these.

Table 3: Year of Establishment of National PV Centre

S.No.	Country	Year of Establishment of National PV Centre
1.	Tanzania	1989
2.	Ghana	1999
3.	Nigeria	2004
4.	India	2005
5.	Uganda	2005
6.	Zanzibar	2005
7.	Madagascar	2006
8.	Cambodia	2008
9.	Rwanda	2008
10.	Kenya	2009

Source: Interviews of NRAs

Designated staff: Staff for PV at the NRAs in developing countries is mostly in single digits,

(average of 5 staff per country) and although this fulfills the WHO requirements, it is not enough to conduct comprehensive PV. A notable outlier amongst the developing world countries is Thailand, which has 15 staff devoted full time to PV. The responsibilities of the staff are mainly ADR form distribution, report collection, data entry, data analysis for signal detection, communication and administrative work.

Stable basic funding: The PV budget for most of the developing countries was less than \$100,000 (range \$40,000 to \$180,000); USFDA's CBER product safety budget exceeds \$100 million

Collaborating with WHO Programme: All the developing countries assessed are collaborating with WHO and are currently full members or associate members (Cambodia, Rwanda, Zanzibar)

4.2 Assessment of Requirement 2:

ADR form: All the NRAs have a nationally approved ADR reporting form, which is same for all the diseases, except Kenya and Tanzania which also has a simplified ADR form for the private sector.

4.3 Assessment of Requirement 3:

A National Database: Since all the countries are members of the WHO ADR Monitoring programme, they also have access to the WHO safety database, and WHO's Vigiflow software for reporting ADRs. Although it was not indicated as a minimum requirement, many African countries highlighted poor internet connectivity as one of the technological challenges.

An assessment of the number of ADR reports collected since the time of inception showed a range from zero (Cambodia, Rwanda, both of which are relatively new PV centers) to several hundred thousand (Thailand). Most countries reported less than 1000 reports.

4.4 Assessment of Requirement 4:

An advisory committee: Most countries have a Safety Review Committee (SRC) which provides technical assistance on PV. The exceptions are Madagascar, Rwanda and Zanzibar. In contrast the SRA have several committees which advise on vaccines and therapeutics related safety issues.

4.5 Assessment of Requirement 5:

A communication strategy: Various methodologies are employed by NRAs to communicate with their stakeholders—these include newsletters, conferences, websites, publications, mass media, and targeted

messages. One country indicated they employ all the approaches (Uganda), while several countries didn't respond to this question (Cambodia, Madagascar, India).

Besides these activities, there are several programs that lay special emphasis on specific disease areas, for example, in Madagascar the PV programs focused on malaria. In Tanzania, the program is focused on malaria, HIV, AIDS, tuberculosis and immunization. In Ghana, the focus is on malaria, HIV/AIDS, immunization, medication errors and rational use of drugs. In Kenya it is focused on malaria and immunization.

In Thailand, the Thai FDA monitors adverse reactions through the National Health Product Vigilance Center (HPVC). The monitoring system includes passive event monitoring post-licensing (mandatory for newly registered products) as well as intensive monitoring (cohort event monitoring) for some products such as herbal products, antiretroviral and anti-tuberculosis medicines, and H1N1 pandemic influenza vaccines. Reporting during clinical trials of imported medicines is in the process of being defined, and the IND unit of the Drug Control Division takes responsibility for analysis of this information. The Department of Disease Control in the Bureau of Epidemiology takes responsibility for the monitoring of vaccine-related events and coordinates with Thai FDA for their analysis.

With respect to vaccines, besides Thailand, two other developing countries with relatively advanced regulatory systems were studied as part of this report, either through their websites, or through direct contact with regulatory staff: Brazil and India. All three national regulatory authorities oversee products that are prequalified by WHO; in the case of vaccines this means that the NRA activities, including safety monitoring, both pre- and post-marketing, have been assessed by WHO and found to meet established criteria.

In India there is provision for adverse event monitoring during clinical trials and for reporting spontaneous reports during PMS, after marketing, all of which is described in its regulations²⁴.

Brazil sets out requirements in a recently published document,²⁵ which includes safety monitoring in clinical trials, post-marketing surveillance, and the submission of PV plans early in the development cycle. In the case of vaccines, Brazil has a well-developed surveillance system through the national immunization program, which in fact was the first to pick up cases of viscerotropic effects with yellow fever vaccine.

In conclusion, it is clear that most of the PV departments in developing countries have minimal capacity to perform comprehensive risk management and are not in a position to enforce the conduct of PV.

As stated in chapter 2, MAHs consider PV as a cost center, and tend to perform PV activities only superficially when PV is not enforced or accompanied with strong regulations. This creates a dilemma for PDPs—how involved should PDPs be in ensuring *effective* PV activities are conducted by their partner organizations. This point is discussed in more depth in chapters 5 and 6.

Chapter 5: Assessment of PV activities in PDPs

5.1 General background of PDP products

PDPs are developing an estimated 43 vaccines, 30 drugs and 14 diagnostic products,²⁶ some of which are expected to reach the market by 2021. The most common diseases/conditions being targeted by the PDPs are malaria, neglected tropical diseases, tuberculosis, diarrhea and HIV/AIDS; all have knowledge of safety monitoring in clinical trials, but, except for HIV/AIDS, there is limited knowledge related to PMS.

The PDP Access Steering Committee categorized timelines for product pipelines (Table 4).

²⁴ [http://cdsco.nic.in/html/schedule-y%20\(amended%20version-2005\)%20original.htm](http://cdsco.nic.in/html/schedule-y%20(amended%20version-2005)%20original.htm)

²⁵ See <http://portal.anvisa.gov.br/wps/portal/anvisa/posuso/farmacovigilancia> (in Portuguese)

²⁶ Published in the PDP Access Strategy Discussion Paper October 2010; shows data up to June 2009

Table 4: Status of vaccines and therapeutics that have been launched or are in the pipeline ²⁷

	Already launched or have been submitted for approval	2014-2016	2018	2021
Vaccines	6	11	8	18
Therapeutics	7	5	6	11

PDPs that have the maximum number of vaccine candidates in the pipeline in various stages of clinical development are PATH Vaccine Solutions (9 vaccines), IAVI (9 vaccines), DVI Consortium (based at IVI) (7 vaccines) and PATH Malaria Vaccine Initiative (MVI) (1 vaccine candidate and approximately 4 translational projects). For therapeutics, the most prolific PDPs are MMV (12 products) and DNDi (11 products).

5.2 State of PV in PDPs

Awareness and importance

The majority of PDPs consider PV important and critical, and all the PDPs are aware of their obligations with regards to PV activities in clinical trials, which is not surprising since most of their products are in clinical development. By regulation the responsibility for reporting adverse events during clinical trials and also post-marketing rests with the sponsor or MAH. However, many PDPs are also overseeing these activities as part of their role in product development, and they intend to stay involved to set the stage for safety monitoring following product introduction.

“We invest considerable time up front preparing PV plans for each of our [clinical] studies...” (IDRI).

“PV will surely be needed because this product is going to be used on healthy population and therefore it becomes important to ensure that it does not cause any harm to the healthy individuals” (IPM).

“PV is considered vital for these products” (IPM).

“Yes, post-marketing PV is a very important area for us, but, given where we are in development, we have not yet invested a great deal of resources in it. We plan to conduct demonstration/Phase IV studies in a few countries and are developing strategies for this now.” (TB Alliance)

“MMV recognizes the critical importance of PV in ensuring that post-launch, products that we have helped co-develop continue to demonstrate the same safety...” (MMV)

PDPs and their potential role in PV

All PDPs were actively involved in PV during clinical trials, and consider it to be their responsibility—either alone or in partnership with other stakeholders (pharma/vaccine development partner, contract research organization (CRO), NRA or WHO).

Table 5 presents a summary of vaccines, their development stages, regulatory strategies and the stakeholder planning to take major responsibility for PV. It is clear that the stage of product development and the regulatory strategy have a major impact on the level of involvement that the PDP will have in PV activities.

Table 5: Vaccine PDPs – Products, Development Stages, Regulatory Strategies, PV Responsibility

PDP	Products	Stages	Regulatory Strategy	PV Responsibility
Infectious Disease Research Institute (IDRI)	Leishmania vaccines (2)	Preclinical to 1-2	IND phase 1 in US, technology transfer, licensing and distribution from developing country manufacturer	Principal investigators responsible for trial reporting but PDP ensures that all requirements are met
Dengue	Dengue	Preclinical to	Development in endemic	Sponsors generally

²⁷ Data source: Snapshot of PDP portfolios published in the PDP Access Strategy Discussion Paper October 2010 plus the interviews conducted as part of this report.

PDP	Products	Stages	Regulatory Strategy	PV Responsibility
Vaccine Initiative Consortium (DVI)	vaccines (6)	2B-3	countries and licensed there or technology transfer for licensing in endemic country or multinational development with endemic country trials	responsible for reporting but PDP active in guidelines development for phase 4 trials and NRA capacity building
Malaria Vaccine Initiative (MVI)	Malaria vaccines (~ 20 projects)	Preclinical to 2B-3	Multinational development with endemic country trials for most advanced product, others may be facilitated development and/or technology transfer possibly with US FDA IND as well as endemic country trials	PV is generally the responsibility of the sponsor, with PDP involvement.
AERAS	Tuberculosis vaccines (4)	Preclinical to 2B-3	Facilitated development with endemic country trials	PDP responsible for all trials up to proof of concept, and reporting to FDA/EMA; afterwards will be responsibility of ultimate manufacturer
PATH Vaccine Solutions (PATH)	Influenza vaccines (4)	Preclinical to 4	Facilitated development and/or technology transfer with endemic country trials and licensing, distribution from developing country manufacturer	In general PV will be the responsibility of partner organization but in some cases PATH holds IND and is responsible. Will be engaging a CRO for this
	Rotavirus vaccines (3)	Preclinical to 2B-3		
	Pneumococcal conjugate vaccines (4)	Preclinical to 2B-3		
	ETEC vaccines (3)	Preclinical to 2B-3		
	Shigella vaccines (1)	Preclinical to 1-2		
Meningitis Vaccine Project (MVP)	Meningitis A conjugate vaccine (1)	Preclinical to 4, introduction	Technology transfer with manufacture and licensure in India with endemic country trials, WHO prequalification	PDP has taken overall responsibility in collaboration with the manufacturer
GAVI Accelerated Vaccine Introduction (AVI)	Pneumococcal conjugate vaccines (2)	4, Introduction	Multinational development, WHO prequalified, introduction into endemic countries	Responsibility generally with the manufacturer
	<i>Haemophilus influenzae</i> conjugate vaccines (as pentavalent) (6)	Introduction		
	Rotavirus vaccines (2)	Introduction		

Some examples of PDP activity in the clinical phase illustrate how the regulatory strategy can influence activities. For the malaria vaccine developed by GSK and the Sanofi Pasteur dengue vaccine, the PDPs involved, MVI and DVI Consortium, respectively, have been involved in the safety monitoring aspects of the clinical trials from the point of view of participating in meetings with WHO oversight groups, although it is the MAH that does the reporting.

AERAS philosophy is to take products to proof of concept and then hand over to a manufacturer who will go forward to phase 3 trials, production, licensing and marketing. Currently they are still in preclinical up to phase

1-2 trials, which are being carried out in endemic countries. As their products fall under FDA or EMA oversight, PV activities in all trial stages will be done to the highest level, also with the involvement of the local NRAs where the trial is done.

Similarly, IDRI invests considerable time up front preparing PV Plans for each of their studies, and reportable adverse events are distributed in a timely fashion to the medical monitor, to the Data Safety Monitoring Boards, and to the FDA.

The DVI Consortium (DVI) has been quite active in more generic approaches, and has developed guidance documents for clinical trials, which have been approved by WHO's Expert Committee on Biological Standardization. DVI has also been involved in building capacity by sponsoring meetings with regulatory authorities in developing countries where clinical trials are planned to discuss issues related to clinical trial approval, clinical trial inspections, and specific questions on the application and the product.

The DVI Consortium work plan provides for the development of guidelines for Phase 4 studies to be used by sponsors and by regulatory authorities in approving such studies. It is intended that WHO will convene a form of representatives from the vaccine industry, regulators, and PV experts, and to also request inputs from the GACVS. Another DVI initiative, which will apply to all trials including post-marketing, is to develop guidelines on AE reporting which will cover case and severity definitions, frequency of evaluation and duration of follow-up. The case definitions may be modeled on those developed by the Brighton Collaboration. This will allow comparison across products and trials.

Table 6: Therapeutic PDPs – Products, Development Stages, Regulatory Strategies, PV Responsibility

PDP	Products	Stages	Regulatory Strategy	PV Responsibility
Concept Foundation	Contraceptives and other reproductive health products	Registered	ICH-compliant dossiers to local RAs and WHO prequalification	Regulatory affairs manager at the PDP would handle it as and when required.
Drugs for Neglected Diseases Initiative (DNDi)	Drugs for Malaria, Human African Trypanosomiasis, Visceral Leishmaniasis, Chagas disease.	Drug discovery - Phase 4	Twinned, Article 58 for NCEs, local RA for combos of already registered products	Pharma partners handle most of the PV and post marketing surveillance activities. Project director and Medical Director of the program are responsible for PV at the PDP.
Global Alliance for TB Drug Development (TB Alliance)	TB drugs	Drug discovery - Phase 3	SRAs with or without WHO prequalification	MAH will have major responsibility for PV
The Institute for One World Health (iOWH)	Leishmaniasis, Malaria, Diarrheal diseases, Soil Transmitted helminthiasis	Drug discovery – 4	-	iOWH has not been asked to do PV by the NRAs but conducts PV activities. Once the launch occurs the manufacturer is then responsible for PMS/PV activities.
International Partnership for Microbicides (IPM)	HIV/AIDS	Preclinical-phase 2 (<i>Will start phase 3 in mid 2011</i>)	Article 58 for new API/delivery system, FDA to facilitate PEPFAR procurement	Presently reporting is done to clinical medical officer in clinical Safety Department at the PDP.
Medicines for Malaria Venture (MMV)	Malaria	Drug discovery-Phase 4	SRA with or without WHO prequalification	MMV works with partners to develop appropriate RMP for products

In the case of PMS, most PDPs were clear that it was not their responsibility or mandate, but were not clear about their continued involvement in the process. Some considered that the MAH was fully responsible and

their responsibility ended once the product was approved; others felt an ethical responsibility to stay involved but were not sure how to engage with their partner. Some were keenly aware of their partners' activities in PMS, while others didn't know what their partner was doing, or capable of doing.

There was interest from PDPs to know how others are handling this technical area--*"Interesting to know how other PDPs are dealing with PMS. Want to know how they handle the risk and share in this activity."*

Examples of some responses:

"Our role is more of a facilitator in developing the combination product. Countries national programs that adopt these products should be responsible for doing safety work and PV work." [DNDi]

"MMV works with partners to develop appropriate RMP for products." [MMV]

"Our pharma partners handle most of the PV and post marketing surveillance activities." DNDi

"Once the launch occurs, the manufacturer is then responsible for PMS/PV activities – however not discussed in depth or carved out for the moment" [iOWH]

"Technically, in most cases post-marketing PV is part of mandate for our pharma partners, but we are also interested to support post-marketing PV and to learn more about WHO, PDP and other activities to strengthen post-marketing PV globally. In the case where the TB Alliance has the rights to the drug, we ourselves will be responsible for ensuring post-marketing PV, but this drug is still quite far from market." [TB Alliance].

"We are not the owner of these products. We consider PV execution as our ethical responsibility. Converting these responsibilities to execution is a problem, we can't do it totally by ourselves" (DNDi).

For most PDPs, the general undercurrent is that their responsibility ends with the authorization of the products. The expectation then is that the MAH should therefore invest and be accountable for fulfilling PV obligations to the regulator as well as to ensure patient safety.

The involvement of the PDPs in PMS depends on their partner organizations, which include CROs, pharmaceutical companies (multinational and local) and WHO.

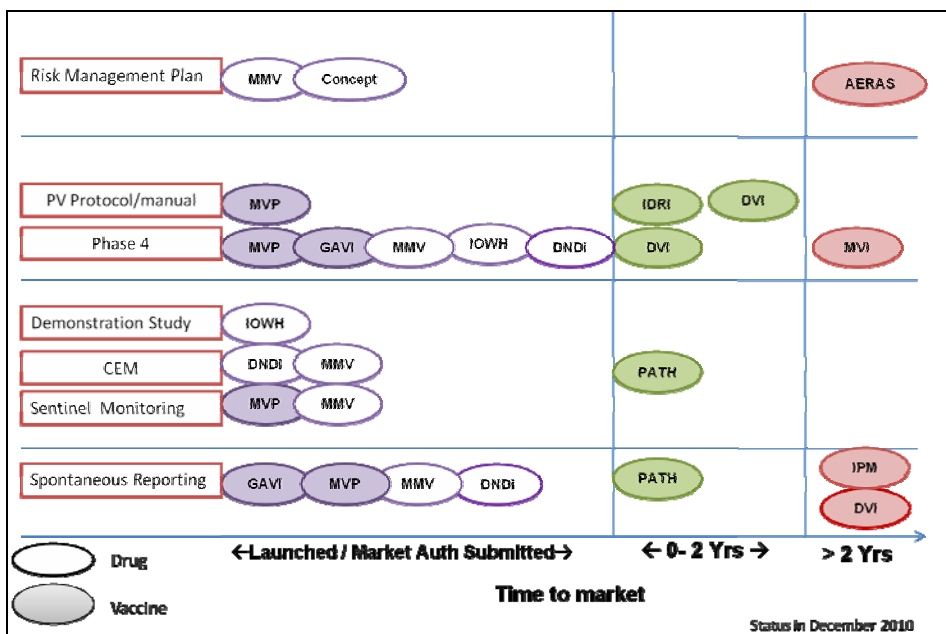
When the MAH is a multinational corporation (MNC) pharmaceutical or vaccine company, the PDPs seem to play a less involved role, often expecting that the MNC partner has the capacity to conduct the required PMS studies. The PDPs also acknowledged that even though pharma/vaccine partners may be managing PV activities at the moment, but there are limitations to the methodology that is being followed. As one PDP indicated, *"Though pharma partners are handling most of the post-marketing PV activities, the voluntary reporting systems may not be as robust in countries of interest to PDPs. We are interested to know what ideas there are for strengthening post-marketing PV in high TB burden countries, particularly systems that can work across disease areas for greater efficiency"* [TB Alliance].

Mapping PMS activities of PDPs

The study assessed the various types of PV activities being conducted or being planned by the PDPs for products that have been launched (or for products where market authorization dossier has been submitted); for products that are likely to reach the market in the next 2 years; and for products that are more than 2 years from market. The objective was to assess the level of activity in each of the categories.

Not surprisingly, most of the activities are focused on the first column, however, what is surprising is the dearth of planned activities for the second two columns.

Figure 2: Activities planned or being conducted by PDPs for post-marketing surveillance



PV activities for products that have been launched (or if dossier has been submitted for market authorization)

There are an estimated 12 products that fall in this category. As expected, the PDPs that have their most advanced product already launched or submitted for authorization seem to be more active in preparing for or implementing post authorization PV activities. MMV, iOWH, MVP, DNDi and AVI have either planned or are undertaking multiple activities for products that they have already launched in the market. For products in the introduction phase, particularly in the case of vaccines, there is intense PDP involvement in PV studies, development of guidelines and standards for PV monitoring, and in-country capacity building activities to ensure comprehensive AE reporting of newly introduced products.

Specifically, for Coartem dispersible tablets, which were jointly developed by Novartis and MMV, there has been spontaneous reporting and a phase IV study. Sanofi-Aventis is conducting cohort event monitoring for 15,000 patients on artesunate-amodiaquine, in partnership with DNDi and MMV in Ivory Coast. iOWH (not its pharmaceutical partner, Gland), is conducting phase 4 studies on Paromomycin IM injection in India, Bangladesh & Nepal.

PV activities for products that are 0-2 years from market launch

There are an estimated 9 products that fall in this category, but few organizations, viz. IDRI, DVI, and PATH, indicated their current or planned efforts for post-marketing surveillance.

Activities for products that are more than 2 years from market launch

There are over 50 products under development, which are more than 2 years away from launch. However, only 4 organizations, viz. AERAS, IPM, MVI and DVI, indicated their current or planned efforts for PMS.

5.3 Assessment of type of PV activities being planned

Numerous scientific approaches are employed to collect safety information in PV. From the previous figure it is evident that phase 4 trials are the most commonly employed strategy by PDPs, and have been proposed across all segments.

The phase 4 studies for therapeutics have been conducted with partner pharmaceutical companies – e.g. Novartis with MMV, Sanofi-Aventis with DNDi.

For the vaccines there are various examples of phase 4 studies being planned in collaboration with WHO and the NRAs. Some of the interesting developments in this regard are:

In Dec 2009, MVP presented their meningococcal A conjugate vaccine introduction plan to WHO's Global Advisory Committee on Vaccine Safety (GACVS), providing them a full review of all the safety data in almost 9000 clinical trial participants. The GACVS concluded from the documentation and safety analysis there was no indication that the product had safety issues. However to increase the power of detection it was proposed to do a PV study in the first three introduction countries, a population of 200,000-400,000. PV protocols were developed with the assistance of WHO and the NRAs in the three countries. The PV studies were done in Sept 2010. The data from the first cut of the safety data were to be presented to GACVS in December 2010.

Along with GSK, MVI is in the planning stages for a phase 4 study on the most advanced malaria vaccine, and met with WHO's Joint Technical Expert Group of the Global Malaria Programme and Integrated Vaccine Research with representatives from EMA and African NRAs to consider the first draft of a protocol.

AVI is conducting a large introduction study of a prequalified pneumococcal vaccine that is furnished in 2-dose vials without preservative to determine if such a presentation can be used safely in developing countries. The vaccine was prequalified with the restriction that it would be used only in a controlled manner with formal post-introduction monitoring. This study is being carried out in Kenya. The study is an observational study, there are three main outcomes (1) injection site reaction within 7 days; (2) sepsis within 48 hours; (3) death within 7 days.

Spontaneous reporting is also quite popular, probably because it is a powerful method for signal generation, relatively inexpensive to implement, and commonly used in developing countries.

Interestingly, none of the PDPs discussed the development of a pregnancy registry.

Some PDPs like MVP, MMV, DNDi, AVI and PATH have either adopted or are planning to adopt multiple methodologies for post authorization PV.

Since RMPs are a requirement by the EMA and US FDA, those PDPs that are planning to obtain European and US approval are automatically required to develop these plans.

5.4 PV and Regulatory Authorities

Practically all the products developed by PDPs are targeted at developing countries. And as discussed in chapter 4 most SRAs of developing countries have embryonic PV departments. Some of the countries where the PDPs intend to introduce their products include: Africa – *Morocco, Kenya, Sierra Leone, Rwanda, Gambia, Mali, Nigeria, and Burkina Faso*; Sudan, *Ethiopia, Uganda, DRC, Mozambique, South Africa*; Asia – *India, Indonesia, Nepal, Bangladesh, Thailand*; Latin America – *Brazil*.

However, several PDPs have decided to register their products with SRAs (or get approvals from SRAs) in order to ensure the highest level of safety and efficacy. SRAs insist on more stringent PV planning and implementation and, as a result, PDPs with products under review by SRAs are better informed and more aware of the PV responsibilities.

Countries which are considered to have non stringent NRAs often have minimal PV requirements. DVI, which is planning to register products in dengue endemic countries, states "*[there is] no technical capacity in these NRAs for AE. They receive applications and get advice from consultants, and may contact WHO. Thailand and Brazil are exceptions.*" [DVI]

To help build capacity of NRAs in PV, DVI convened a meeting that included regulatory authority and ethics committee representation from all ten ASEAN countries, plus four south Asian countries, Bangladesh, India, Sri Lanka, and Pakistan, NRAs and ECs, to consider issues in clinical trial approval and oversight including safety monitoring.

Sometimes, the standards being followed are different for developed and developing countries for the same product.

5.5 HR Capacity for PV in PDPs

For PV in clinical trials one or more of the following specialists were typically involved – Medical Director, Medical Monitor, Senior Medical Manager, Project Director, Clinical Unit Head. It was difficult for PDPs to attribute the amount of time these professionals spent on PV activities, especially since PV is an integral part of clinical trials. The level of effort for PMS was easier to allocate.

None of the PDPs has a dedicated PV specialist for PMS activities yet. This was not surprising, as in many cases, the products are still in early clinical development.

However, several organizations are investing time to build PV capacity and training their staff. Some specific examples of PDPs HR capacity is described below:

HR in Therapeutic PDPs

IPM reported that for their early clinical trials reporting is done to a clinical medical officer in the Clinical Safety department, but they will scale up infrastructure for phase 3 and will create a unit for PV activity. The clinical department currently includes 7 full time equivalents (FTEs).

iOWH has a Senior Medical Manager and Medical Monitor in-house and has outsourced CRO Medical Monitors for particular studies, all of whom have received PV training and have worked on GCP clinical trials. Their responsibilities include review of SAE reports, site visits, ensuring that all SAEs are properly documented and reported to the relevant authorities, and communicating with the DSMB members. The in-house positions are now based in India where much of the clinical trial work is going on. The annual budget for PV activities is about \$225,000, included in the general clinical trial budget.

Concept Foundation has a regulatory affairs manager, who is a pharmacist with knowledge and industry experience in PV—this individual would handle PV as and when required, although that has not been required up to now, possibly because reporting is being done by the MAH.

HR in Vaccine PDPs

Virtually all vaccine PDPs interviewed reported some staff resources for PV. For MVI, the head of the clinical unit is the contact person on PV related issues. The PDP expects that most PV issues will be the responsibility of the sponsor and the Data Safety Monitoring Boards (DSMBs).

IDRI has three clinical and regulatory staff persons, who are investing about 5% of their time to handle PV activities. Their responsibilities include writing the PV plan for each study, receiving any incoming reports from study sites within 24 hours, distributing the report to the Medical Monitor and DSMB, coordinating discussion of the event, submission of reports to FDA and ensuring submission of reports as well to local and national authorities. The budget for PV is covered under clinical staff salaries.

AERAS has one staff member in clinical safety, one additional staff member who manages the safety database, and two additional people to handle documentation, which amounts to about 2 FTEs in-house. Reporting is outsourced. Their clinical trial budget is about \$18M per year of which the safety budget is probably about \$120-150 k for each product. This includes DSMBs, safety monitoring, and Serious Adverse Event (SAE) processing.

PATH Vaccine Solutions has a Clinical and Regulatory Department, which oversees phase 1 and 2 trials, but counts on sponsors and manufacturers to take charge of most of the PV activities. To expand the portfolio of trials, a CRO for PATH will be engaged before the end of this year to assist in setting up PV.

MVP has one PV lead plus one FTE per site for SAE reporting for clinical trials. As WHO was an integral part of the PDP, training and capacity building were built into the budget.

5.6 PV Capacity in countries and the role of PDPs

Several of the PDPs discussed capacity building approaches that might be useful to build NRA capacity in PV. IOWH mentioned the possibility of formal PV training workshops focusing on different national requirements which would be useful for NRAs in the countries they were working. As mentioned above, 2 vaccine PDPs, MVP and DVI, are promoting NRA capacity building in PV as part of their activities. It is perhaps no accident that both of these PDPs have WHO as an integral partner. MVP and DVI have both worked with WHO to sponsor workshops with NRA representatives and ethics committees in which clinical trials were to be held to build capacity for CT approval and oversight, including PV reporting. MVP, as part of its PV study, included NRA staff from the 3 countries where these studies were performed to help draft the study protocols. DVI has developed guidelines that have now been adopted by WHO's Expert Committee on Biological Standardization on the characteristics and manufacture of dengue vaccines, which will aid NRAs in reviewing licensing dossiers; DVI is now developing guidelines for Phase 4 trials to address specific safety issues that might be connected with dengue vaccines.

Chapter 6: Analysis of challenges and suggested approaches

6.1 Major challenges in conducting PV

6.1.1 PDPs

- Role of PDPs: there is a need to define the role of PDPs specifically in PMS—and accordingly provide the necessary resources (financial, human and technical)
- Synergy: There is minimal sharing of information and resources between PDPs. Although PDPs are in varying stages of product development, some synergies can already be exploited, some of which are defined further below – sharing information on country norms, on regional or country laboratory parameters, sharing CROs for reporting of events, etc.
- Internal PV capacity is non-existent or weak, especially for PMS.
- Financial: PMS activities and technical information can be expensive and have not been funded (PV within clinical trials is less of an issue).
- Follow up of PMS: PDPs may not be able to access PMS data since all reports are collected by the MAH. Provision should be made to ensure that MAH share these reports, or findings of these reports with PDPs.
- There is a lack of standardization in clinical trial case definitions, time of onset, severity, which makes comparisons across trials in a specific type of products difficult, especially since regulatory authorities tend to address each product individually.

6.1.2 Sponsors/MAH/Pharmaceutical or Vaccine Manufacturer

- MAH might not conduct PMS, especially in countries where PV regulations do not exist or are not enforced
- MAH may not have the capacity or funding to do PMS.

6.1.3 National Regulatory Authorities—SRA and non-SRA

SRA

- In some cases, industrialized country agencies (NRAs, IRBs) involved in oversight of clinical trials in developing countries may require activities that are not appropriate or not applicable. In addition, this double oversight could lengthen the time for approval of products

Non SRA

- In several countries, there is no clear requirement from NRAs for PMS
- Lack of enforcement by the NRA results in poor adherence to policy by MAH
- There may not be sufficiently trained regulatory staff to do case analysis
- Once a product is licensed, it is difficult to stimulate spontaneous reporting.
- Regulatory authorities often fail to provide regular on adverse events to health care professionals and consumers.

6.2 Solutions

There are some obvious approaches that can be conducted by PDPs:

Challenges relating to PDPs:

- Clearly define the roles and responsibilities of PDPs with respect to the entire PV life-cycle, which could be used as a basis for partnership agreements between PDPs and manufacturers
- Develop joint and generic approaches that can be leveraged by the various PDPs. For example, a PDP Reference Handbook describing successful strategies in countries for different types of products, or specific regulatory hurdles, could be of use. Another area for synergy would be to develop prevalence

of common PV-related diseases, such as Guillain-Barré Syndrome or Stevens-Johnson syndrome in Africa, as well as standard biological markers for such diseases in specific populations.

- Ensure sufficient funding is available for PV and specifically PMS, with a separate line item (activity-based costing); in addition explore strategies of cost sharing between PDPs. In the area of computerized data management, AERAS suggests some synergies could be attained by using a common service provider, which would save on the cost of software and also of writing the Standard Operating Procedures regarding electronic reporting. Another possibility for lowering cost would be to use the same clinical trial sites, including Phase 4 sites, which the PDPs could “plug into” with their particular products, and where the infrastructure would already be developed. PV studies could allow also smaller nested studies at the same sites to generate additional data.
- Build capacity of staff so that they clearly understand the entire life-cycle of PV—from clinical trials to PMS
- Ensure PDPs have legal right over the PMS data being gathered by MAH and/or have the right to ensure the MAHs are conducting PMS.
- Develop standard definitions for outcomes, perhaps based on Brighton Collaboration terms, as part of general trial guidelines.

Challenges relating to sponsors/MAH/pharmaceutical or vaccine manufacturers

- Ensure that PDPs are more involved in ensuring implementation of PV by MAHs
- Include specific PMS activities in the contract with MAH
- Conduct an assessment of PV capacity of sponsor at the time of contract signing and closer to the time of product launch. Ensure MAH builds the necessary capacity prior to product launch.

Challenges relating to NRA (SRAs and non-SRAs) and their PV departments to:

- Build capacity of NRAs, which may include development of policies, provision of training, establish systems for sharing of information, etc. This can be conducted in collaboration with WHO, UMC and other technical organizations already working with NRAs.

Chapter 7: Concluding Remarks

As discussed in Chapter 1, PV is a critical component of acceptability, which in turn is a critical component of access. Interviews also indicated that WHO may require PV to be conducted before it will include the product in the 'prequalification list', which means that PV may also become a critical component of affordability, which is a vital component of access. In other words, '*no pharmacovigilance = no access.*'

Although in principle, it is obvious that PV should be conducted, there is tension in achieving this goal due to mis-aligned incentives of the key stakeholders, viz. PDPs, MAHs (pharmaceutical/vaccine companies) and NRAs.

PDPs: The main goal of the PDP is to promote public health, and as one PDP said, 'PV execution is our ethical responsibility'. However, most PDPs clearly indicated that PV is not their mandate; they don't have the funds; and anyway it is the responsibility of the MAH. As another PDP stated, 'converting [ethical] responsibilities to execution is a problem.' Generally PDPs don't continue to stay engaged in the PMS process and do not request safety findings from their partner organizations. One PDP also responded that they didn't have the legal right to these data as it is confidential.

Sponsors/MAHs are the organizations that are legally responsible for conducting PV. However, PV is considered as a cost centre, and if it isn't enforced, it doesn't get done. It is quite common for sponsors to be highly active in conducting PV for an SRA, but the same sponsor for the same product may not conduct PV activities in non SRA countries. In addition, there are some sponsors that do not have the capacity to conduct PV, have never done it before, and therefore must build this capacity.

In many cases, PDPs were unaware of the level of preparation and the degree of PV resources that the partner pharmaceutical company has deployed to fulfill its safety obligations on an ongoing basis.

NRA: The NRAs in developing countries often do not have the capacity to do PV and do not enforce PV (there are exceptions, such as Brazil, Thailand). As a result, PMS in developing countries normally does not get implemented with the same level of rigor, if at all.

While PV is always conducted during clinical trials, it is not always conducted after the product is launched. PDPs must explore strategies that will ensure implementation of PMS--because, without pharmacovigilance, access is compromised.

Next steps:

Although many of the PDPs are quite familiar with PV, the PDP group as a whole needs to become more knowledgeable about the importance of PV for their respective products; they need to be aware of the potential impact they can have—at the regional, national level and the grass-roots level (of the target market); but most importantly, they need more clarity regarding their roles and responsibilities in PV, especially in PMS.

This can be achieved through the hosting of a joint consultation of all relevant PDPs—vaccine and drug PDPs; PDPs with products on the market and PDPs that are still several years away from market authorization. The consultation should include specialists from the technical organizations (as listed in chapter 3), PV specialists from NRAs and PDP's research partners. The end point of the consultation (and some additional deliberations post-consultation) should lead to some general and some specific recommendations regarding the objectives, roles, challenges, activities, timelines and budgetary implications of PDPs in PV.

ACRONYMS

ACT	Artemisinin-based Combination Therapies
ADR	Adverse Drug Reaction
AE	Adverse Event
AEFI	Adverse Event Following Immunization
ASAO	Artesunate Amodiaquine
AVI	Accelerated Vaccine Introduction Project of GAVI
CBER	Center for Biologics Evaluation & Research
CEM	Cohort Event Monitoring
CIOMS	Council for International Organizations of Medical Sciences
CRO	Contract Research Organization
CT	Clinical Trial
CTs	Clinical Trials
DNDi	Drugs for Neglected Diseases initiative
DRMP	Developmental Risk Management Plan
DSMB	Data Safety Monitoring Boards
DVI	Dengue Vaccine Initiative
EC	Ethics Committee
EMA	European Medical Agency
ETEC	Enterotoxigenic Escherichia Coli
FDA	Food and Drug Administration
FTE	Full Time Equivalent
GACVS	Global Advisory Committee on Vaccine Safety
GAVI	Global Alliance for Vaccines and Immunization
GSK	GlaxoSmithKline
HIV / AIDS	Human Immunodeficiency Virus/ Acquired immune Deficiency Syndrome
HPVC	Health Product Vigilance Center
ICH	The International Conference on Harmonization
ICSR	Individual Case Safety Report
IDRI	Infectious Disease Research Institute
INESS	The INDEPTH Effectiveness and Safety Studies
iOWH	Institute for One World Health
IPM	International Partnership for Microbicides
ISoP	The International Society of Pharmacovigilance
IVB	Department of Immunization, Vaccines and Biologicals (WHO)
JHPHS	John Hopkins Bloomberg School of Public Health
M&E	Monitoring and Evaluation
MAH	Marketing Authorization Holder
MMV	Medicines for Malaria Venture
MNC	Multinational Corporation
MVI	Malaria Vaccine Initiative
MVP	Meningitis Vaccine Project
NCE	New Chemical Entity
NRA	National Regulatory Authority
PASS	Post Authorization Safety Study
PDP	Product Development Partnership
PLH	Product License Holder
PMS	Post-marketing Surveillance
PV	Pharmacovigilance
PvPI	Pharmacovigilance Program of India
RMP	Risk Management Plan
SAE	Serious Adverse Event
SRA	Stringent Regulatory Authority
SRC	Safety Review Committee
TB Alliance	Global Alliance for TB Drug Development
UMC	Uppsala Monitoring Centre
UNESCO	United Nations Educational, Scientific and Cultural Organization
VAERS	Vaccine Adverse Event Reporting System
WHO	World Health Organization
WHOART	WHO Adverse Reaction Terminology

Appendix 1: People interviewed

PDP Therapeutics

Organization	Contact person	Position
Drugs for Neglected Diseases Initiative (DNDi)	Nathalie Strub-Wourgaft	Clinical Development Director
TB Alliance Drug Development (TB Alliance)	Elizabeth Gardiner	Vice President, Market Access
Medicines for Malaria Venture (MMV)	George Jagoe	Executive Vice-President ,Global Access
	Stephan Duparc	Chief Medical Officer, Science
	David Ubben	Director, Clinical Development Science
The Institute for One World Health (IOWH)	Rhonda Sarnoff	Director, Monitoring and Evaluation (M&E) and Field Research
	Sonali Kochhar	Medical Director
Concept Foundation	Peter Hall	Chief Executive Officer
International Partnership for Microbicides (IPM)	Thomas Mertenskoetter	Former Executive Director External Relations
	Ron Nardi	Chief of Regulatory Affairs

PDP Vaccine

Organization	Contact person	Position
Infectious Disease Research Institute (IDRI)	Jill Ashman	Senior Clinical Research Manager
	Aude Frevol	Senior Clinical Research Associate
Aeras Global TB Vaccine Foundation	J.Bruce McClain	Chief Medical Officer, Clinical Affairs
Meningitis Vaccine Project (MVP)	Marc Laforce	MVP Director, PATH
Pediatric Dengue Vaccine Initiative(PDVI) / DVI	Richard Mahoney	Director, Vaccine Access
	Joaquim Hombach	WHO focal point, Immunization, Vaccines and Biologicals, World Health Organization
	Anna Durbin	Assistant Professor , JHPHS
PATH Malaria Vaccine Initiative(MVI)	Didier Leboulleux	Associate Director, RTSS Clinical Unit
	Julia Nunes	Program Officer Product Development and Access
Hib Initiative/PneumoADIP	Lois Privor-Dumm	Director, Vaccine Access & Implementation
	Danny Feikin	Epidemiologist -
PATH projects	Jorge Flores	Clinical and Regulatory Affairs

Technical Organization

Organization	Contact person	Position
World Health Organization (WHO)	Shanthi Pal	Acting Manager Pharmacovigilance, Quality Assurance and Safety: Medicines
WHO Collaborating Centre for Advocacy and Training in Pharmacovigilance, Accra	Issifu Acheampong	-
	Alex Dodoo	Director, Centre for Advocacy and Training in Pharmacovigilance
WHO Vaccine Safety Team	Patrick Zuber	Head, Vaccine Safety Team
UMC (WHO Collaborating Centre for International Drug Monitoring)	Jerry Labadie	Vaccine Safety Specialist
	Sten Olsson	WHO Officer
UMC Africa	Alex Dodoo	Director

National Regulatory Authority

Country	Contact person	Position
United States	Dan Salmon	Vaccine Safety, National Vaccine Program Office
	Robert Ball	Director, Office of Biostatistics and Epidemiology ,CBER, FDA
Canada	Carole Legare	Manager, Medical Section, Marketed Health Products Directorate
European Union	Priya Bahri	Pharmacovigilance Lead for Guidelines and Risk Communication
Thailand	Wimon Suwankesawong	Head of Health Product Vigilance Center (HPVC), Technical and Planning Division
Cambodia	Va Sokea	Vice chief of Essential Drug Bureau
Ghana	Nartekuo Nartey-Armooh	-
Kenya	Jayesh Pandit	Head- Department of Pharmacovigilance
Madagascar	Donat P. E. Rakotomanana	Chef du Service de la Pharmacovigilance
Nigeria	Pharm. Adeline Osakwe	Head of National Pharmacovigilance Centre
Rwanda	Nywakira Anicet	Program Associate
Tanzania	Henry Irunde	AG. Manager, Clinical Trials & Pharmacovigilance
Uganda	Helen Ndagize	Head Drug Information Department
Zanzibar	Mohammed Omar M.Simba	Focal person pharmacovigilance
India	Professor YK Gupta	Coordinator, Pharmacovigilance Program of India (PvPI)

Misc

Bill & Melinda Gates Foundation	Patricia Atkinson	Senior Program Officer, Global Health Delivery
	Vincent Ahonkhai	Senior Program Officer, Global Health Delivery
Global Health Technology Coalition	Kaitlin Christenson	

Appendix 2: Scope of work

The Challenge of Pharmacovigilance While Ensuring Equitable Access to

New Health Products in Low Income Countries

INTRODUCTION:

Objective:

The overall goal is to enhance the effectiveness and efficiencies of PDPs and to contribute to the knowledge base of PDP access work

Purpose:

The purpose of this discussion paper is to explore and document PDP experiences and challenges with regard to pharmacovigilance, with an emphasis on documenting the different strategies taken by various PDPs and accompanying rationales behind decisions to utilize those strategies.

OUR APPROACH & METHODOLOGY

The approach for this research/consultancy would be as follows:

- Link access and pharmacovigilance and provide the necessary context of this research
- Summarize the key pharmacovigilance strategies deployed by NDRA/National Vaccine Centers, including distinction between: developed and developing countries; drugs (NCE and generic) vs. vaccines vs. biologicals vs. chemicals vs. medical products; capacity of pharmacovigilance in various countries
- Within the above context, conduct interviews with relevant PDPs (e.g. diagnostics do not play a role here) and provide a summary of the findings, highlighting strengths and weakness in the approaches taken by the PDPs
- Conduct interviews with NDRAs (Pharmacovigilance Department) of some countries to assess their pharmacovigilance capacity (policy, activities, HR, etc); with specific questions related to the various dosage forms being developed by the PDPs
- The important element of this research is to ensure that this work is conducted within the framework of 'Access' and within the context of the target countries that need these products, as opposed to a standalone exercise focused only on pharmacovigilance.

The following table outlines steps in the project:

Project steps

Step 1	<ul style="list-style-type: none">• Prepare outline of final paper/deliverable to client (get OK)
Step 2	<ul style="list-style-type: none">• Develop short brief on global PV strategies and link between access & PV
Step 3: Interview with PDPs (approx 15)	<ul style="list-style-type: none">• Develop discussion guide/questionnaire with input from client• Send the questionnaire, accompanied with a short background note on PV strategies to the interviewee ahead of time• Conduct interviews• Write up detailed interview notes• Assess and extract key findings from the interviews• Conduct follow up interview for clarifications and additional information
Step 4: Interview with sample countries (approx 5-10)	<ul style="list-style-type: none">• Develop discussion guide/questionnaire with input from client• Send the questionnaire, accompanied with a short background note on the consultancy to the interviewee ahead of time• Conduct interviews• Write up detailed interview notes• Assess and extract key finding from the interviews• Conduct follow up interview for clarifications and additional information
Step 5	<ul style="list-style-type: none">• Do an assessment of leading global PV organizations that conduct research, training, capacity building
Step 6: Report writing	<ul style="list-style-type: none">• Write report and submit (Draft 1)• Get feedback from client• Write and submit final report

Appendix 3: Definitions and terminologies in pharmacovigilance²⁸

The following definitions are used in the WHO Programme for International Drug Monitoring and member countries are encouraged to utilize them. Most of these definitions have been incorporated into guidelines issued by the ICH, EMEA and other competent national authorities. Full details, comments and explanatory notes for these are available from the Uppsala Monitoring Centre (<http://www.who-umc.org/DynPage.aspx?id=13111&mn=1513>).

Pharmacovigilance

The science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problems. Source: *The Importance of Pharmacovigilance, WHO 2002*

Adverse Reaction

"A response to a drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function." - WHO Technical Report No 498 (1972)

Unexpected Adverse Reaction

An adverse reaction, the nature or severity of which is not consistent with domestic labelling or market authorization, or expected from characteristics of the drug.

Adverse Event / Adverse Experience

Any untoward medical occurrence that may present during treatment with a pharmaceutical product but which does not necessarily have a causal relationship with this treatment.

Side Effect

Any unintended effect of a pharmaceutical product occurring at doses normally used in man which is related to the pharmacological properties of the drug.

Signal

Reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously. Usually more than a single report is required to generate a signal, depending upon the seriousness of the event and the quality of the information.

Serious Adverse Event or Reaction

A serious adverse event or reaction is any untoward medical occurrence that at any dose:

- results in death
- requires inpatient hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability/incapacity
- is life-threatening

To ensure no confusion or misunderstanding of the difference between the terms "serious" and "severe", the following note of clarification is provided:

The term "severe" is not synonymous with serious. In the English language, "severe" is used to describe the intensity (severity) of a specific event (as in mild, moderate or severe); the event itself, however, may be of relatively minor medical significance (such as severe headache). Seriousness (not severity) which is based on patient/event outcome or action criteria serves as guide for defining regulatory reporting obligation.

²⁸ www.pvafrika/pvtoolkit (note, link maybe temporarily broken as the site is being migrated to this destination)

Appendix: 4 Pharmacovigilance Methods²⁹

Several methods can be used to collect safety information in pharmacovigilance. In all national pharmacovigilance systems, SPONTANEOUS REPORTING forms the bedrock of the system despite its well-known limitation of under-reporting. It is relatively inexpensive and provides a life-time monitoring of all medicines in all patients in any healthcare system. There are other systems including active patient follow-up e.g. Cohort Event Monitoring (CEM). Brief highlights of the various pharmacovigilance methods are given below (adapted from the ICH E2E Guideline. The full document can be downloaded from the ICH website using this link <http://www.ich.org/cache/compo/276-254-1.html>.

Passive Surveillance

Spontaneous reports

A spontaneous report is an unsolicited communication by healthcare professionals or consumers to a national pharmacovigilance centre, pharmaceutical company, regulatory authority or other organization (e.g., WHO, Regional Centres, Poison Control Centre) that describes one or more adverse drug reactions in a patient who was given one or more medicinal products and that does not derive from a study or any organized data collection scheme.

Spontaneous reports play a major role in the identification of signals of drug related problems once a drug is marketed. They can also provide important information on at-risk groups, risk factors, and clinical features of known serious adverse drug reactions. Caution should be exercised in evaluating spontaneous reports, especially when comparing drugs. The data accompanying spontaneous reports are often incomplete, and the rate at which cases are reported is dependent on many factors including the time since launch, pharmacovigilance-related regulatory activity, media attention, and the indication for use of the drug.

Case series

Series of case reports can provide evidence of an association between a drug and an adverse event, but they are generally more useful for generating hypotheses than for verifying an association between drug exposure and outcome. There are certain distinct adverse events known to be associated more frequently with drug therapy, such as anaphylaxis, aplastic anemia, toxic epidermal necrolysis and Stevens-Johnson Syndrome. Therefore, when events such as these are spontaneously reported, it is important that pharmacovigilance centres place more emphasis on these reports for detailed and rapid follow-up.

Stimulated Reporting

Several methods have been used to encourage and facilitate reporting by health professionals in specific situations (e.g., in-hospital settings) for new products or for limited time periods¹. Such methods include on-line reporting of adverse events and systematic stimulation of reporting of adverse events based on a pre-designed case definition. Although these methods have been shown to improve reporting, they are not devoid of the limitations of spontaneous reporting, especially selective reporting and incomplete information.

Active Surveillance

Active surveillance, in contrast to spontaneous reporting, seeks to ascertain completely the number of adverse events via a continuous pre-organised process. An example of active surveillance is the follow-up of patients treated with a particular drug as in Cohort Event Monitoring. Patients who fill a prescription for this drug may be asked to complete a brief survey form and give permission for later contact. In general, it is more feasible to get comprehensive data on individual adverse event reports through an active surveillance system than through a spontaneous reporting system.

Sentinel sites

Active surveillance can be achieved by reviewing medical records or interviewing patients and/or physicians in a sample of sentinel sites to ensure complete and accurate data on reported adverse events from these sites. The selected sites can provide information, such as data from specific patient sub-groups, that would not be available in a spontaneous reporting system. Further, information on the use of a drug, such as abuse, can be targeted at selected sentinel sites. Some of the major weaknesses of sentinel sites are problems with selection bias, small numbers of patients, and increased costs.

Drug event monitoring

Drug event monitoring is a method of active pharmacovigilance surveillance. In drug event monitoring, patients might be identified from electronic prescription data or automated health insurance claims. A follow-up questionnaire can then be sent to each prescribing physician or patient at pre-specified intervals to obtain outcome information. Information on patient demographics, indication for treatment, duration of therapy (including start dates), dosage, clinical events, and reasons for discontinuation can be included in the questionnaire. Limitations of drug event monitoring can include poor physician and patient response rates and the unfocused nature of data collection, which can obscure important signals. In addition, maintenance of patient confidentiality might be a concern. On the other hand, more detailed information on adverse events from a large number of physicians and/or patients might be collected. A modification of Drug Event Monitoring is Cohort Event Monitoring (CEM), an active pharmacovigilance method promoted by the World Health Organisation and other agencies.

Cohort Event Monitoring

Cohort Event Monitoring is very similar to Drug Event Monitoring. In CEM, patients on a particular drug or groups of drugs are recruited at time of initiation of antiretroviral therapy (ART) and followed up by way of clinic or home visits or where appropriate by phone calls. A pre-treatment questionnaire is filled at time of recruitment and post-treatment questionnaires are filled at times of follow up which may either be once e.g. for anti-malarials or life long e.g. for anti-retrovirals. CEM also includes specific pregnancy questionnaires. A complete Standard Operating Procedure for CEM is given in the appendices to this toolkit.

Registries

A registry is a list of patients presenting with the same characteristic(s). This characteristic can be pregnancy (pregnancy registry), a disease (disease registry) or a specific exposure (drug registry). Each type of registry, which only differ by the type of patient data of interest, can collect a battery of information using standardised questionnaires in a prospective fashion.

Comparative Observational Studies

²⁹ www.pvafrika/pvtoolkit (note, link maybe temporarily broken as the site is being migrated to this destination)

Traditional epidemiologic methods are a key component in the evaluation of adverse events. There are a number of observational study designs that are useful in validating signals from spontaneous reports or case series. Major types of these designs are cross-sectional studies, case-control studies, and cohort studies (both retrospective and prospective)

Cross-sectional study (survey)

Data collected on a population of patients at a single point in time (or interval of time) regardless of exposure or disease status constitute a cross-sectional study. These types of studies are primarily used to gather data for surveys or for ecological analyses. The major drawback of cross-sectional studies is that the temporal relationship between exposure and outcome cannot be directly addressed. These studies are best used to examine the prevalence of a disease at one time point or to examine trends over time, when data for serial time points can be captured. These studies can also be used to examine the crude association between exposure and outcome in ecologic analyses. Cross-sectional studies are best utilized when exposures do not change over time.

Case-control study

In a case-control study, cases of disease (or events) are identified. Controls, or patients without the disease or event of interest, are then selected from the source population that gave rise to the cases. The controls should be selected in such a way that the prevalence of exposure among the controls represents the prevalence of exposure in the source population. The exposure status of the two groups is then compared using the odds ratio, which is an estimate of the relative risk of disease in the two groups.

Cohort study

In a cohort study, a population-at-risk for the disease (or event) is followed over time for the occurrence of the disease (or event). Information on exposure status is known throughout the follow-up period for each patient. A patient might be exposed to a drug at one time during follow-up, but non-exposed at another time point. Since the population exposure during follow-up is known, incidence rates can be calculated. In many cohort studies involving drug exposure, comparison cohorts of interest are selected on the basis of drug use and followed over time. Cohort studies are useful when there is a need to know the incidence rates of adverse events in addition to the relative risks of adverse events. Multiple adverse events can also be investigated using the same data source in a cohort study. However, it can be difficult to recruit sufficient numbers of patients who are exposed to a drug of interest (such as an orphan drug) or to study very rare outcomes.

Phase IV studies³⁰, often called Post Marketing Surveillance Trials, are conducted after a drug or device has been approved for consumer sale. Pharmaceutical companies have several objectives at this stage: (1) to compare a drug with other drugs already in the market; (2) to monitor a drug's long-term effectiveness and impact on a patient's quality of life; and (3) to determine the cost-effectiveness of a drug therapy relative to other traditional and new therapies. Phase IV studies can result in a drug or device being taken off the market or restrictions of use could be placed on the product depending on the findings in the study

Targeted Clinical Investigations

When significant risks are identified from pre-approval clinical trials, further clinical studies might be called for to evaluate the mechanism of action for the adverse reaction. In some instances, pharmacodynamic and pharmacokinetic studies might be conducted to determine whether a particular dosing instruction can put patients at an increased risk of adverse events. Genetic testing can also provide clues about which group of patients might be at an increased risk of adverse reactions. Furthermore, based on the pharmacological properties and the expected use of the drug in general practice, conducting specific studies to investigate potential drug-drug interactions and food-drug interactions might be called for. These studies can include population pharmacokinetic studies and drug concentration monitoring in patients and normal volunteers.

Descriptive studies

Descriptive studies are an important component of pharmacovigilance, although not for the detection or verification of adverse events associated with drug exposures. These studies are primarily used to obtain the background rate of outcome events and/or establish the prevalence of the use of drugs in specified populations.

Natural history of disease

The science of epidemiology originally focused on the natural history of disease, including the characteristics of diseased patients and the distribution of disease in selected populations, as well as estimating the incidence and prevalence of potential outcomes of interest. These outcomes of interest now include a description of disease treatment patterns and adverse events. Studies that examine specific aspects of adverse events, such as the background incidence rate of or risk factors for the adverse event of interest, can be used to assist in putting spontaneous reports into perspective. For example, an epidemiologic study can be conducted using a disease registry to understand the frequency at which the event of interest might occur in specific subgroups, such as patients with concomitant illnesses.

Drug utilization study

Drug utilization studies (DUS) describe how a drug is marketed, prescribed, and used in a population, and how these factors influence outcomes, including clinical, social, and economic outcomes. These studies provide data on specific populations, such as the elderly, children, or patients with hepatic or renal dysfunction, often stratified by age, gender, concomitant medication, and other characteristics.

³⁰ <http://www.centerwatch.com/clinical-trials/overview.aspx>

Author's biographies

Paul S. Lalvani

Paul Lalvani is the founder of the RaPID / O3i Pharmacovigilance Program, a multi-country initiative that provides targeted capacity building support in Vigiflow training. It operates in partnership with Swiss Tropical and Public Health Institute (University of Basel), University of Ghana, UMC-A, and other partners in developed and developing countries.

Paul is the Director and Dean of the Empower School of Health, New Delhi, which conducts degrees and diploma programs in clinical research and pharmacovigilance in collaboration with University College London and the Uppsala Monitoring Centre. His area of expertise is in assessing and building capacity of health professionals, public health programs and national pharmacovigilance centers. Empower School of Health has been instrumental in providing technical assistance to India's 'new and improved' Pharmacovigilance Programme of India (PvPI) and the establishment of a new coordinating centre at All India Institute of Medical Sciences, India, under the guidance of Professor Y K Gupta.

Empower School of Health has also provided support to PDPs (non-profit drug/vaccine research organizations funded by Gates Foundation and other donors), to conduct a mapping of their pharmacovigilance needs and has provided recommendations of possible solutions.

Paul has 20 years of experience in healthcare and management and has advised various Ministries of Health, The Bill and Melinda Gates Foundation, Roll Back Malaria Partnership, Northwestern University's Kellogg School of Management, etc. He has held senior positions at the Global Fund (Geneva) and Management Sciences for Health (Wash DC). He has published work in the International Society of Pharmacovigilance (ISoP) Journal, Malaria Journal, and has delivered lectures in ISoP, various Ministries of Health (Nigeria, Uganda, India, Tanzania and more), UN meetings, and technical organizations.

In addition to his pharmacy degree, Paul holds a master's degree in business administration (MBA) from Northwestern University's Kellogg School of Management, Chicago.

Contact details: Paul Lalvani : paul.lalvani@empower.net.in

Julie Milstein

Julie B. Milstien, Ph.D, is an independent consultant in vaccine supply and regulatory issues. She is also an Adjunct Professor, University of Maryland School of Medicine in Baltimore, MD USA Department of Geographic Medicine, where part of her work relates to regulatory issues in vaccine development, including work with the Dengue. Vaccine Initiative. She is retired from the World Health Organization where her responsibilities included planning and coordinating activities related to supply, financing and quality of vaccines and immunization-related technologies in global immunization programmes. Before joining the World Health Organization in 1988, she worked for the Food and Drug Administration of the United States of America for 14 years, where her area of responsibility included vaccine research, review of vaccine licensing applications, and evaluation of adverse reactions for biological and some pharmaceutical products.

Contact details: Julie Milstien: jmilstien@gmail.com