



**A Report of the
Safety and Surveillance
Working Group**

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Executive Summary

Drugs and vaccines are reaching unprecedented numbers of people in low- and middle-income countries (LMICs). These products have tremendous potential to save lives and reduce suffering, but many of the countries in which these products will be used do not have the capacity to effectively monitor their post-market safety. International initiatives have sought to address this gap, but have not attracted significant donor or industry support, or political capital and resources from LMIC governments. With new donor funding scarce in this weak global economy, substantial new resources for addressing post-market safety needs may not be forthcoming. Given limited resources and expanding post-market safety needs, a new strategy is needed. This report is the culmination of the seven-month effort of the Safety Surveillance Working Group (SSWG) to develop that strategy.

The strategy developed through the SSWG process is designed to complement and build upon, not duplicate or replace, existing international pharmacovigilance capacity building initiatives, World Health Organization (WHO) standards and technical assistance programs, and disease- and product-specific initiatives. The human and financial resources available to strengthen post-market safety surveillance in developing countries are limited. Synergies must be encouraged and reinforced.

This strategy developed through the SSWG process has five parts, which are summarized here.

Early focus on the global health product pipeline

A wide variety of drugs and vaccines are now reaching patients in LMICs, including novel medications, generic and traditional medicines, and substandard, spurious, falsely labeled, falsified, and counterfeit drugs. All require adequate post-market safety surveillance, which does not yet exist in most of these countries. This report recommends, however, focusing on pharmacovigilance for the novel or newly introduced drugs and vaccines that will be launched in developing countries through global health programs, such as the GAVI Alliance and Global Fund to Fight AIDS, Tuberculosis, and Malaria, in the next decade. This pipeline includes products for use in resource-poor populations in LMICs for HIV/AIDS, malaria, tuberculosis, cervical cancer, family planning, and the dozen other parasitic, soil transmitted, bacterial, and tropical infections known as ‘neglected diseases.’ The reasons for focusing on the global health product pipeline are fourfold.

First, the drugs and vaccines in the global health product pipeline will be provided to the world’s poorest and most vulnerable people. Second, developing country regulators will not be able to rely on the safety and benefit-risk assessments conducted in developed countries for these drugs and vaccines since most will be launched exclusively or simultaneously in LMICs. Third, post-market safety surveillance needs for the candidate drugs and vaccines in the global health pipeline are relatively predictable and quantifiable because data exist on their projected distribution, which makes preemptive planning and action to ensure adequate oversight possible. Finally, global health programs offer potential partnerships, resources, and expertise that may be used to build sustainable LMIC pharmacovigilance systems better capable of supporting benefit-risk management of global health products and the other drugs and vaccines in use in these markets.

Risk-based Prioritization

Global health programs are projected to introduce dozens of potentially lifesaving drugs and vaccines into LMICs over the next decade. This report recommends prioritizing the post-market safety surveillance needs of the global health product pipeline on the basis of the likely and anticipated safety risk of the candidate drugs and vaccines, the proximity of their projected launch dates, and the pharmacovigilance capacity of the countries in which the product will be introduced.

This report applies these proposed risk-based criteria to the later-stage candidate products in the global health product pipeline (phase II or later), which are expected to be introduced into LMICs within the next decade. This analysis represents a snapshot in time, based on the incomplete data currently available to the authors. Its projections are likely to change as new and more complete data emerge, candidate products progress through clinical development, and attrition occurs in the pipeline. Based on the current data, the following observations emerge:

- Few of the countries projected to host the greatest number of higher-risk drug and vaccine introductions over the next decade have functional pharmacovigilance systems.
- However, most of the countries that will host such introductions have some minimal pharmacovigilance structures that may be leveraged to support product introduction and build that capacity. Building post-market safety surveillance in such settings is feasible.
- Many of the projected product launches will occur in the same countries. The iterative nature of these introductions suggests the need to build sustainable post-market safety surveillance systems in these countries as part of these product introductions. Otherwise, each new product introduction will need to establish pharmacovigilance infrastructure anew.
- Many of the higher-risk drug and vaccine introductions will occur in East Africa, West Africa, and South Asia. This clustering suggests the possibility for cooperative approaches and pooling of resources to improve post-market safety surveillance in these regions.

Inverting the current capacity building paradigm

The focus of international pharmacovigilance capacity building initiatives has been establishing a minimum capacity in all countries to conduct passive safety surveillance and, as these systems improve, enhancing the capacity of regulators and public health programs to implement active surveillance. Passive surveillance alone, however, cannot be relied upon to identify post-market safety concerns of novel and newly introduced drugs and vaccines in LMICs with poor infrastructure, low reporting, and limited data on background population rates on adverse events.

Pharmacovigilance capacity building initiatives cannot achieve sustained improvements by investing in what effective pharmacovigilance programs and institutions *look like*, rather than what they will need to *do* in the LMIC settings. Accordingly, this report recommends inverting the traditional capacity building paradigm by leveraging the pharmacovigilance conducted in support of novel or newly introduced drugs and vaccines as a means of catalyzing sustainable and broadly functional post-market safety surveillance systems. These programs should be designed in cooperation with the local regulatory authority, incorporate local stakeholder input, and reflect local capabilities.

Incorporating Sustainability from Outset

The need for increased support for post-market safety surveillance in LMICs may seem bottomless, but the resources available to meet that need are not. Pharmacovigilance campaigns conducted in support of new product introductions must be designed to stretch the limited resources available and leave capacity behind for future introductions and addressing other priority post-market safety needs. This report outlines strategies to achieve this objective including leveraging existing infrastructure, ensuring investments support both drug and vaccine post-market safety surveillance, and supporting cooperative and regional approaches.

Pharmacovigilance campaigns must be designed from the outset to generate industry and local government buy-in. As an operational matter, effective risk identification, assessment, mitigation, and communication requires the commitment and cooperation of local regulators, health professionals, public health officials, and industry stakeholders to succeed. As a funding matter, donor investments in improving pharmacovigilance capacity in LMICs will be limited in duration and amount. This report recommends more emphasis on pharmacovigilance in global health programs; engaging local governments and stakeholders in the conception and implementation of pharmacovigilance campaigns; and employing matching grants and other financial incentives to attract more local government investment.

Planning for Scalability

Given limited resources and pressing needs, initiatives to strengthen post-market safety surveillance in LMICs must be prioritized, but should be scalable to address broader health needs of these countries and their populations. The novel and newly introduced drugs and vaccines that will be introduced in developing countries over the next decade are by no means the only pharmacovigilance challenges that these countries face.

This report proposes several strategies for improving the scalability of initiatives to strengthen post-market safety surveillance in LMICs. Promoting data sharing and management as part of pharmacovigilance campaigns fosters the timely identification of drug and vaccine safety concerns and improves efficiency. Investments in training and infrastructure should be done in a manner that lays the foundation for addressing broader drug and vaccine safety concerns.

Ensuring predictable and sustainable funding for training, infrastructure, and staff is essential for establishing scalable post-market safety surveillance systems. This report proposes establishing an international funding mechanism that includes a multi-donor trust fund to provide short-term, catalytic funding to priority countries seeking to establish post-market safety surveillance; a co-financing arrangement with local governments based on their economic status that encourages local ownership; and the establishment of industry fees to ensure sustainability.

Donor and industry funding will not be forthcoming or sustained, however, without improving and demonstrating the effectiveness of post-market safety surveillance in developing countries. Accordingly, post-market safety surveillance strengthening initiatives must be subject to monitoring, evaluated, and adjusted to respond to deficiencies in performance and local demands.

Toward Implementation

The way forward on strengthening post-market safety surveillance in LMICs is not to define the particular combination of pharmacovigilance techniques that should be applied in every country, drug, or vaccine. Stakeholders must recognize that adequate post-market safety surveillance in LMICs is critical to global health and that global health product introduction represents an important need and opportunity for strengthening that surveillance, but investments must be tailored to the products and countries involved. This report recommends the following measures:

More and better data on the global health product pipeline. Building post-market safety surveillance takes time. More and better data on product introduction projections would allow donors, international technical agencies, and governments to plan, prioritize, and take advantage of the potential synergies that may exist as a result of multiple product introductions. This risk-based pipeline assessment performed in this report should be updated regularly and incorporated into planning.

Increased coordination. Improving coordination in the post-market safety surveillance conducted in support of these product introductions would reduce the need for duplicative investments and exploit potential synergies for building pharmacovigilance in those countries. Donors and programs should work with a small group of national regulatory authorities, technical agencies, PDPs, and industry representatives involved in the forthcoming global health product introductions to adopt common reporting and investigation forms and standardized criteria on the collection, storage, codification, and reporting of safety concerns. These forms and criteria should be simple, feasible for use in most LMICs, and, to the extent possible, based on international norms and standards.

A multi-donor trust fund to support pilot programs. Post-market safety surveillance is new to many LMICs. The strategies outlined in this report for building sustainable and scalable post-market safety surveillance systems are promising, but must be tested by LMIC governments, global health programs, PDPs, and international technical agencies. A multi-donor trust fund should be established for funding such pilots. Contributions should be solicited from all relevant stakeholders; a pooled funding arrangement would help avoid the possible conflict of interest that might otherwise arise. Trust fund resources should be distributed in the form of matching grants to reduce long-term dependence among recipients and ensure stakeholder ownership.

Regional technical facilities. Industry, developed country regulators, and technical agencies have tremendous expertise that could help product sponsors and LMIC regulators implement the strategies outlined in this report. Regional technical advisory facilities should be established to provide this expertise. Intermediary entities, such regional health and economic institutions, should host these facilities and help ensure participation is active. The facility could also function as a center of excellence and facilitate the sharing of safety reports and exchange of benefit-risk management strategies. The multi-donor trust fund resources should support these technical advisory facilities.

The report concludes by outlining the collaboration and investment needed to move toward implementation from key stakeholder groups, including: product sponsors; global health programs; regulatory authorities: donors; industry; and international technical agencies.

Abbreviations

ACSoMP – World Health Organization Advisory Committee on Safety of Medicinal Products

ACT – Artemisinin-based combination therapies

AEFI – adverse events following immunization

AMRH – African Medicines Regulatory Harmonization Initiative

APEC – Asia Pacific Economic Community

ARVs – antiretroviral medicines

ASEAN— Association of Southeast Asian Nations

AVAREF— African Vaccine Regulatory Forum

CIOMS – Council for International Organizations of Medical Sciences

EC – European Commission

EMA — European Medicines Agency

EPI – expanded program in immunization

FDA — U.S. Food and Drug Administration

GAVI — Global Alliance for Vaccines and Immunization

GACVS -- Global Advisory Committee for Vaccine Safety

ICH— International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use

ICSR – individual case safety report

IDMP – World Health Organization Program for International Drug Monitoring

IeDEA – International Epidemiologic Database to Evaluate HIV/AIDS

INDEPTH – International Network for the Demographic Evaluation of Populations and Their Health

JE – Japanese encephalitis

LMICs – low- and middle-income countries

MSH – Management Sciences for Health

NRA — national regulatory authority

PAHO – Pan American Health Organization

PEPFAR – U.S. President’s Emergency Plan for AIDS Relief

PDP — product development partnership

PMI – President’s Malaria Initiative

R&D — research and development

SAGE — World Health Organization Strategic Advisory Group of Experts

SIAPS – Systems for Improved Access to Pharmaceuticals and Services

SSWG - Safety Surveillance Working Group

TB — tuberculosis

UMC – Uppsala Monitoring Center

UNICEF — United Nations Children’s Fund

USAID – U.S. Agency for International Development

WHO — World Health Organization

WHOART – WHO Adverse Reaction Terminology

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This report is the product of the Safety Surveillance Working Group (SSWG), a collaborative effort initiated by the Bill and Melinda Gates Foundation and its industry partners to develop practical and scalable strategies for supporting post-market drug and vaccine safety surveillance in low- and middle-income countries. The process spanned seven months and involved in-person meetings in Seattle, USA; London, UK; and Addis Ababa, Ethiopia. Participants were invited to join in a personal capacity and on a voluntary basis. More than 40 experts and stakeholders participated in one or more SSWG meeting, including representatives from a broad range of donor institutions (10), developing country regulatory authorities (8), industry (7), international technical agencies and intergovernmental institutions (4), developed country regulatory authorities and technical agencies (4), product development partnerships (3), academia (3), and global health policy organizations (2). This report reflects the SSWG discussions, but its participants were not asked to endorse the strategies outlined in this report. A list of participants appears in the annex of this report.

Many individuals contributed information, ideas, and inspiration for this report. We thank, first, the SSWG participants, who devoted their valuable time to thinking through the challenges of strengthening post-market safety surveillance in low- and middle-income countries. Throughout, participants excelled in balancing the interests they were closest to in order to identify solutions that work for all.

Next, we particularly thank the individuals who generously provided the data, analysis, and insights that are the foundation of this report. David Shoultz and Saara Romu at the Bill and Melinda Gates Foundation and Michael Santos and Phillip Klimke of the Boston Consulting Group provided data on the global health product pipeline and endured our many inquiries for clarification. Tony Boni of the U.S. Agency for International Development (USAID) and Jude Nwokike of Management Sciences for Health (MSH) generously shared pre-released copies of their excellent reports on the pharmacovigilance capacity in Africa and Asia. Without the pipeline data and capacity assessments, the risk-based analysis included in this report would have been impossible.

Private interviews and individual correspondence also informed this report. Over the last year, dozens of people offered their advice and expertise on post-market safety surveillance, capacity building, financing models, and the many other topics covered in this report. The authors are indebted to them. A partial list of these individuals is included in the annex of this report. We regret any omissions. We also appreciate the comments on the SSWG project by the participants at Africa Pharmacovigilance 2012 meeting in Nairobi, Kenya in April 2012 and the Global Vaccine Safety Initiative meeting in Hurghada, Egypt in November 2012.

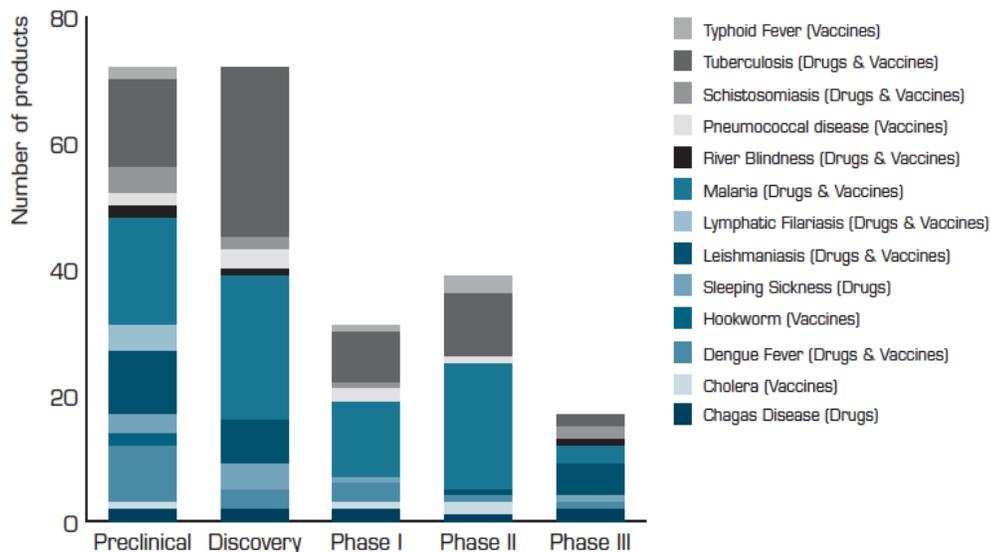
Finally, numerous individuals deserve special thanks for their active engagement and leadership throughout the SSWG project: Vincent Ahonkhai, Lesley Edwards, Jenn Jones, Hannah Kettler, and James Platts of the Bill & Melinda Gates Foundation, and Amrit Ray of Johnson & Johnson. Sophie Gregg, a consultant to the Foundation, has our gratitude for her organizational efforts.

The Challenge

Drugs and vaccines are reaching unprecedented numbers of people in low- and middle-income countries (LMICs). The reasons are twofold.

First, a combination of private philanthropy, government intervention, and investment in product-development partnerships has greatly expanded treatment and immunization programs for the world's poorest people. The GAVI Alliance and its partners have supported the immunization of more than 100 million children in 56 low-income countries annually against tuberculosis (TB), polio, measles, tetanus, yellow fever, and other diseases. The U.S. President's Emergency Plan for AIDS Relief (PEPFAR), the Global Fund to Fight AIDS, Tuberculosis and Malaria (Global Fund), and other programs have likewise extended access to treatment for HIV/AIDS, malaria, and TB to millions.¹ Over the next decade, developing country treatment and immunization programs will expand further to include novel and newly introduced drugs and vaccines.² Millions of children and adults in LMICs may soon be receiving novel, life-saving drugs and vaccines for malaria, TB, dengue fever, cholera, and others.³

Neglected disease product pipeline



¹ World Health Organization, UNAIDS and UNICEF, Towards universal access: Scaling up priority HIV/AIDS interventions in the health sector – Progress Report (2009). Available at:

http://www.who.int/hiv/pub/tuapr_2009_en.pdf; World Health Organization, World Malaria Report (2010). Available at http://www.who.int/malaria/world_malaria_report_2010/en/index.html

² WORLD HEALTH ORGANIZATION, UNICEF, AND WORLD BANK, STATE OF THE WORLD'S VACCINES AND IMMUNIZATION (3d ed. 2010).

³ Developing New Drugs & Vaccines for Neglected Diseases of the Poor: The Product Developer Landscape. <http://www.bvgh.org/LinkClick.aspx?fileticket=h6a0cJK9drg%3d&tabid=91> (accessed August 20, 2012).

Second, rising incomes and the growing burden of non-communicable diseases have increased the demand for medicines in many LMICs.⁴ Government health spending has increased in LMICs generally; countries such as India and China are establishing national health insurance schemes that include drug reimbursement.⁵ For the first time, the working poor in developing countries are a target growth market for international pharmaceutical manufacturers.⁶ Drug sales in emerging markets are expected to nearly double over the next five years, reaching at least \$345 billion.⁷

The drugs and vaccines now reaching LMICs have the potential to revolutionize the health care in these settings, reduce avoidable deaths and infirmity, and afford millions the opportunity to lead productive lives. Achieving that potential will depend, however, on ensuring adequate monitoring of the safety of these medicines post-approval.

The importance of post-market safety surveillance in global health

Given the extensive clinical testing and regulatory scrutiny that occurs pre-market, it may seem surprising that post-market surveillance is necessary to ensure the safe and effective use of a drug or vaccine. Much remains unknown, however, about the risks and benefits of a new drug or vaccine at the time of its marketing approval. The numbers and heterogeneity of the subjects who participate in clinical trials conducted in support of drug or vaccine approval are limited. The duration of clinical trials is relatively short. The subjects are often healthier, less diverse, and take fewer other medications than the broader patient population. Uncommon and latent adverse effects and potential drug-drug interactions may be impossible to identify until a medical product is in widespread use under real-life conditions and for an extended period of time. Conversely, limitations imposed on the use of a drug or vaccine at approval can ultimately prove unnecessary based on data on the product's use in the broader patient population. Evidence of the risks and benefits of drugs and vaccines continue to emerge over the lifecycle of the product.⁸

The post-market uncertainties concerning the benefits and risks of a drug or vaccine extend beyond its inherent properties. The incidence, risk factors, and severity of reactions to a drug or vaccine in one population may differ significantly from another based on environmental and genetic reasons

⁴ PriceWaterhouseCoopers, LLC, *From vision to decision: Pharma 2020* (2012).

⁵ Chunling Lu et al., *Public Financing of Health in Developing Countries: A Cross-National Systematic Analysis*, 375 LANCET 1375, 1379-82 (2010) (reporting that domestic health spending is increasing in absolute terms in LMICs in most regions of the world, particularly in parts of Latin America, the Middle East, and Asia, but less so in sub-Saharan Africa).

⁶ See Shirley S. Wang & Jonathan D. Rockoff, *Drug Research Gets New Asian Focus*, WALL STREET J. (Dec. 14, 2010), <http://online.wsj.com/article/SB10001424052748703531504575623891891473992.html> (reporting Western pharmaceutical firms' efforts to create drugs for diseases prevalent in Asian markets); Avery Johnson, *Drug Firms See Poorer Nations as Sales Cure*, WALL STREET J. (Jul. 7, 2009), <http://online.wsj.com/article/SB124691259063602065.html> (reporting a push by multinational drug firms to sell already developed products to the working poor in middle-income countries).

⁷ Jonathan D. Rockoff, *Big Drug Makers Struggle to Grow in Emerging Markets*, WALL STREET J., Aug. 19, 2012.

⁸ INSTITUTE OF MEDICINE, *THE FUTURE OF DRUG SAFETY: PROMOTING AND PROTECTING THE HEALTH OF THE PUBLIC* (2007).

that can be difficult to predict.⁹ Programmatic errors occur in prescribing, preparing, administering, or taking medicines.¹⁰ Mistakes and shortcuts in manufacturing can result in poor quality products; the risk is higher in substandard, spurious, falsely labeled, falsified, and counterfeit versions of the medicine.

The need for post-market safety surveillance is even greater for the drugs and vaccines used in resource-poor settings. Patient populations are highly vulnerable, with high prevalence of HIV/AIDS, malnutrition, and other confounding infirmities. In the case of a drug or vaccine targeting neglected diseases, the patient populations are frequently pediatric. Pregnant women also need access to life-saving therapeutics, yet the safety of inadvertent or intentional exposures to medicines during pregnancy can only be assessed through post marketing surveillance.¹¹ Even when a drug or vaccine has an established favorable risk-benefit ratio in high-income markets, concerns may arise regarding its use in resource-poor settings.¹² Risks of errors in immunization and treatment may be higher due to limited health systems and few trained health personnel. Substandard, spurious, falsely labeled, falsified, and counterfeit medicines are a significant problem in LMICs with still nascent regulatory systems.

The Importance for Post-Market Safety Surveillance in Global Health

Post-market safety surveillance is essential for global health treatment and immunization programs because:

- (1) Much remains unknown about the risks and benefits of a drug or vaccine at the time of approval, particularly under real world, resource-poor conditions;
- (2) Post-market safety concerns regarding the use of drugs and vaccines extend beyond the inherent risk of these products;
- (3) Without timely and accurate information on safety and effectiveness, poor quality products can unnecessarily harm patients;
- (4) Real or rumored adverse events can undermine public confidence and do lasting damage to treatment and, especially, immunization programs; and
- (5) Safety concerns regarding one drug or vaccine can quickly spread and undermine other immunization and treatment programs.

⁹ Munir Pirmohamed et al., *Pharmacovigilance in developing countries*, 335 *BMJ* 462 (2007).

¹⁰ WHO Policy Perspectives on Medicines—Promoting Rational Use of Medicines: Core Components, available at <http://apps.who.int/medicinedocs/pdf/h3011e/h3011e.pdf>.

¹¹ White NJ, McGready RM, Nosten FH. *New medicines for tropical diseases in pregnancy: catch-22*, *PLoS Med.* 2008 Jun 17;5(6):e133. doi: 10.1371/journal.pmed.0050133.

¹² Manish M. Patel et al., *Intussusception Risk and Health Benefits of Rotavirus Vaccination in Mexico and Brazil*, 364 *N. ENGL. J. MED.* 2283 (2011) (reporting significantly different rates of intussusception from use of the same vaccine in Brazil and Mexico, possibly as a result of the different polio vaccines used in those countries).

The good news is that many adverse events that occur following treatment or immunization are preventable with adequate surveillance, corrective, benefit-risk management actions, and oversight – i.e., pharmacovigilance.¹³ The World Health Organization (WHO) defines pharmacovigilance as “the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or other drug related problems.”¹⁴ Pharmacovigilance incorporates post-market surveillance to detect and report adverse events; post-approval research to investigate product-related health effects, their magnitude and frequency; and benefit-risk management to educate, communicate, and mitigate product-related health risks.¹⁵ The aim of pharmacovigilance is constantly ensuring that the evidence of the potential clinical benefits of a drug or vaccine sufficiently outweighs its potential risks to justify that product’s use in the target population.

However, the failure to adequately monitor, manage, and communicate the post-market risks of drugs and vaccines has significant consequences. First and foremost, patients may suffer unnecessarily from poor quality products, preventable side effects, and avoidable drug-drug interactions. Adverse drug reactions are a significant cause of death and infirmity in developed countries¹⁶ and are thought to already impose a high toll in developing countries as well.¹⁷ Adverse events due to poor product quality, counterfeit products, and inadequate programmatic efforts limit therapeutic efficacy and have led to antimicrobial resistance, for anti-malaria drugs in particular.¹⁸

Second, real or rumored adverse events, when left unaddressed, can undermine public confidence and do lasting damage to a treatment and immunization program. This risk is highest for vaccines and drugs provided presumptively and prophylactically. These products are often provided to otherwise healthy children and infants, expected to be safe, and employed widely to achieve their disease control and eradication goals. Rumors and media reports that are not rapidly and effectively addressed can undermine confidence in a vaccine and lead to poor participation, thwarting the purpose of the immunization program and wasting the scarce resources invested.¹⁹ Similarly, rumors

¹³ Pirmohamed, M., S. James, S. Meakin, et al. 2004. Adverse Drug Reactions as Cause of Admission to Hospital: Prospective Analysis of 18,820 Patients. *British Medical Journal* July 3; 329(7456): 15–19.

¹⁴ WHO Policy Perspectives on Medicines: Pharmacovigilance: Ensuring the Safe Use of Medicines, WHO (Oct. 2004), available at: <http://www.who-umc.org/graphics/7128.pdf>.

¹⁵ Laura B. Faden and Christopher-Paul Milne, *Pharmacovigilance Activities in the United States, European Union and Japan: Harmonic Convergence or Convergent Evolution?*, 63 *FOOD DRUG L.J.* 683 (2008).

¹⁶ Jason Lazarou et al., *Incidence of Adverse Drug Reactions in Hospitalized Patients: A Meta Analysis of Prospective Studies*, 279 *J AM MED ASSOC* 1200 (1998); Jeffrey A Johnson & Lyle J Bootman. *Drug Related Morbidity and Mortality: A Cost of Illness Model*. 155 *ARCH. INTERN MED* 1949-1956 (1995) (estimating the costs of drug related morbidity and mortality in the United States to be more than \$136 billion annually); A Troyen et al., *Incidence of Adverse Events and Negligence in Hospitalized Patients: Results of the Harvard Medical Practice Study I.*, 324 *NEW ENG J MED* 370 (1991).

¹⁷ Global Fund and World Health Organization, *Towards a global strategy on Pharmacovigilance* 5 (2009).

¹⁸ Gaurvika ML, et al., *Poor-quality antimalarial drugs in southeast Asia and sub-Saharan Africa*, 12 *LANCET INFECTIOUS DISEASES* 488 (2012).

¹⁹ In Nigeria, for example, the disruption of the polio immunization program due to widespread but disingenuous safety rumors undermined the global polio eradication campaign and led to resurgence in the disease, undoing years of steady and expensive progress.

or unaddressed adverse events can reduce demand for an otherwise effective and safe drug, leading to losses in confidence in public health programs.²⁰

Last, the post-market safety risks of drugs and vaccines can be systemic. Safety concerns regarding one drug or vaccine quickly can also spread and undermine other immunization and treatment programs. The risks of inadequate pharmacovigilance of novel and newly introduced products are significant for patients, treatment and immunization programs, and local governments alike.²¹ A suspected, but ultimately disproven link between the measles, mumps, rubella vaccine and autism has eroded support for vaccination globally.²²

Adequate pharmacovigilance is essential for ensuring the safety and effective use of the vaccines and drugs reaching patients in LMICs. Causing avoidable death and disability tragically contravenes the fundamental purpose of extending treatment to historically underserved populations in LMICs. Otherwise, the increasingly scarce global health resources invested in treatment and immunizations programs could be wasted and the goal of improved access to quality, efficacious medicines left unmet. The potential public outcry, litigation, and financial and reputational damage that may result from inadequate post-market safety surveillance may deter some funders and manufacturers from investing in global health programs.

Pharmacovigilance in LMICs

In most developed countries, the monitoring of the safety and effectiveness of drugs and vaccine post-approval is mandated in several ways. Holders of a marketing authorization for a drug or vaccine are legally required to collect, investigate, and submit reports of adverse events concerning that product, even if those events occur in other markets.²³ In many developed countries, this obligation extends to health professionals.²⁴ Finally, many developed country regulators have a variety of legal tools with which to manage post-market drug and vaccine safety concerns, including withdrawing approval and mandating labeling changes, notification of health professionals, and post-market studies.²⁵ The European Medicines Agency (EMA), U.S. Food & Drug Administration (FDA), Japanese Ministry of Health & Welfare, and other stringent regulatory authorities require

²⁰ Doodoo A, Adjei S, Couper M, et al. *When rumours derail a mass deworming exercise*. *Lancet*. 2007 Aug 11;370(9586):465-6.

²¹ A recent independent review of fiduciary control and oversight at the Global Fund concluded that “procurement and management of pharmaceuticals and medical products poses larger risks to the Global Fund’s finances, operations, and reputation than any other activity in its business model;” the independent review urged increased and systemic investment to track adverse events in Global Fund treatment programs. *The Final Report of the High-Level Independent Review Panel on Fiduciary Control and Oversight Mechanisms of the Global Fund to Fight AIDS, Tuberculosis, and Malaria* (2011).

²² Robert Chen et al., *Challenges and Controversies in Immunization Safety*, 15 *INFECTIOUS DISEASE CLINICS OF NORTH AMERICA* 1 (2001).

²³ If serious, the marketing authorization holder must investigate and submit the report to the appropriate public health authority within a defined period of time (e.g., 15 days in the United States and EU). BARTON COBERT, COBERT’S *MANUAL OF DRUG SAFETY AND PHARMACOVIGILANCE* (2nd ed. 2012). See, e.g., 21 CFR 314.80(1)(i), (b).

²⁴ See, e.g., National Child Vaccine Injury Act of 1986.

²⁵ See Institute of Medicine, *Ethical and Scientific Issues in Studying the Safety of Approved Drugs*, Committee Report (2012) (describing post-regulatory FDA options).

drug and vaccine developers to submit pharmacovigilance and benefit-risk management plans about how they would assess and manage the risks of new medicines submitted for licensing.²⁶

Developed country health authorities and marketing authorization holders employ a combination of passive and active surveillance and pharmacoepidemiologic approaches to monitor the safety and effectiveness of drugs and vaccines post-approval. Passive safety surveillance involves the collection, investigation, and analysis of the spontaneous reports of adverse events that potentially involve drugs or vaccines.²⁷ Stimulated reporting includes a set of methods such as on-line reporting and pre-determined case definitions in order to encourage and facilitate reporting by health professionals in specific settings for specific products. Active surveillance includes the use of sentinel sites, drug or cohort monitoring, and disease and pregnancy registries to systematically improve the quality and comprehensiveness of adverse event reporting. Comparative observational studies use traditional epidemiological methods and may involve retrospective case-control or cohort studies using electronic medical records or health insurance databases. Targeted clinical trials that have a primary endpoint of safety are also used to assess the mechanism of adverse reactions when significant risks are identified in pre-approval clinical trials.

Developing countries have historically been able to rely upon the comprehensive post-market safety surveillance that exists in developed countries to identify the risks and benefits of drugs and vaccines. Few novel drugs and vaccines were developed to address the health needs of poor countries. Access to treatment in these settings was limited. Accordingly, with scarce resources and a multitude of pressing public health challenges, many LMICs invested little in drug and vaccine regulatory systems and even less in post-market drug and vaccine safety surveillance.²⁸ A significant minority of LMICs have no post-market safety systems at all.²⁹

As the availability of drugs and vaccines has increased, many developing countries have recently begun to adopt post-market safety systems.³⁰ Progress is occurring, but has been slow. An analysis of 55 LMICs found that most of the countries surveyed lacked sufficient legal mandate to compel adverse event reporting by marketing authorization holders and health professionals and dedicated

²⁶ The EU Guidelines on Pharmacovigilance for Medicinal Products for Human Use specifies the need for pharmacovigilance plans and indicates that post-authorization safety studies (PASS) may be required either as a commitment at the time of authorization or in the post-authorization phase to further assess a signal. The US FDA Modernization Act allows FDA to require postmarketing studies or clinical trials at the time of approval or after approval based on new safety information, with criteria defined in the statute.

²⁷ Philippe Duclos, *A global perspective on vaccine safety*, 22 VACCINE 2059 (2004).

²⁸ In 1997, only 37 (19%) of WHO's 190 Member States, mostly in developed countries, had a reliable, fully functioning national regulatory authority. STATE OF THE WORLD'S VACCINES AND IMMUNIZATION, *supra* note 2.

²⁹ Olsson S, Pal S, Stergachis A, Couper M. An analysis of pharmacovigilance activities in 55 LMICs. *Drug Safety*. 2010;33:689-703; WORLD HEALTH ORGANIZATION, ASSESSMENT OF MEDICINES REGULATORY SYSTEMS IN SUB-SAHARAN AFRICAN COUNTRIES: AN OVERVIEW OF FINDINGS FROM 26 ASSESSMENT REPORTS (2010).

³⁰ Paul Lalvani and Julie Milstien, PDP Access Steering Committee White Paper, Access to New Health Products in Low Income Countries and the Challenge of Pharmacovigilance (2011) (assessing 13 developing countries – India, Brazil, Cambodia, Thailand, Rwanda, Nigeria, Uganda, Madagascar, Kenya, Ghana, Tanzania, Uganda, Zanzibar – and reporting that eight of the ten countries which have established pharmacovigilance centers had done so in the last ten years); Kuemmerle A, Doodoo AN, Olsson S, et al. Assessment of global reporting of adverse drug reactions for anti-malarials, including artemisinin-based combination therapy, to the WHO Programme for International Drug Monitoring. *Malar J*. 2011 Mar 9;10:57.

few staff and had little or no budget for pharmacovigilance.³¹ A recent Strengthening Pharmaceutical Systems study of pharmacovigilance in sub-Saharan Africa similarly found that fewer than 30 percent of the 42 countries surveyed had legal mandates for post-market safety surveillance reporting.³²

With limited resources, legal authority, and tradition of pharmacovigilance, adverse event reporting rates are low in many developing countries. A recent assessment of the safety reports transmitted to the WHO global Individual Case Safety Reports (ICSR) (Vigibase) database found that the high-income countries generate, on average, 130 adverse drug reactions reports per million inhabitants per year, but lower middle-income countries produce 12 annual reports per million inhabitants, and low-income countries produce 3 annual reports per million inhabitants.³³ WHO reports that only 8 of the 26 sub-Saharan African countries that participate in WHO Program for International Drug Monitoring collected adverse event reports in 2010.³⁴ The vast majority of the 55 countries in the 2010 study generated fewer than 1000 individual case safety reports (ICSRs) annually and a third produced fewer than 100 ICSRs per year.³⁵

Irregular and infrequent spontaneous reporting make it difficult to generate signals of potential adverse events connected to a drug or a vaccine, or to respond to real or rumored adverse events.³⁶ For example, from 2001-2008, only a total of 60 ICSRs suspecting ACTs have ever been submitted to the WHO global ICSR database.³⁷ Further, many developing countries lack sufficient infrastructure to assess causality, evaluate the incidence and risk factors of adverse events, make meaningful comparisons with prior experience or calculate the attributable risk of an adverse event.³⁸

Despite recent progress, pharmacovigilance systems in LMICs remain inadequate to address the challenges posed by expanding treatment and immunization.³⁹ The avenues for remedying this deficiency are presently limited. Reliance on safety surveillance from developed countries will not be

³¹ Olsson et al., *supra* note 29. See also Lavani and Milstien, *supra* note 30 (assessing pharmacovigilance in 13 developing countries and reporting that the countries which had pharmacovigilance programs dedicated an average of 5 staff and less than \$100,000 annually to them).

³² Strengthening Pharmaceutical Systems (SPS) Program, Safety of Medicines in Sub-Saharan Africa: Assessment of Pharmacovigilance Systems and their Performance (2011). Submitted to the US Agency for International Development by the Strengthening Pharmaceutical Systems (SPS) Program. Arlington, VA: Management Sciences for Health; Olsson et al., *supra* note 29.

³³ Lise Aagaard, Johanna Strandell, Lars Melskens, Paw S.G. Petersen, and Ebba Holme Hansen, Global Patterns of Adverse Drug Reactions Over a Decade: Analyses of Spontaneous Reports to VigiBase, *Drug Saf* 2012; 35 (12): 1171-1182.

³⁴ WORLD HEALTH ORGANIZATION, ASSESSMENT OF MEDICINES REGULATORY SYSTEMS IN SUB-SAHARAN AFRICAN COUNTRIES: AN OVERVIEW OF FINDINGS FROM 26 ASSESSMENT REPORTS (2010).

³⁵ Olsson et al., *supra* note 29. See also Sampada S. Vaidya et al., *Overview and Comparison of Postmarketing Drug Safety Surveillance in Selected Developing and Well-Developed Countries*, 44 *DRUG INFORMATION JOURNAL* 519 (2010).

³⁶ World Health Organization, *The World Medicines Situation: Pharmacovigilance and Safety of Medicines* (2011).

³⁷ Kuemmerle et al, *supra* note 30.

³⁸ WHO Global Advisory Committee on Vaccine Safety (GACVS), *Global safety of vaccines: strengthening systems for monitoring, management and the role of GACVS*, 8 *EXPERT REV VACCINES* 705 (2009).

³⁹ Bakare N, Edwards IR, Stergachis A, et al. Global pharmacovigilance for antiretroviral drugs: contrasting priorities impair progress. *PLoS Medicine*. Published online 2011 July 5. doi: 10.1371/journal.pmed.1001054.

an option for drugs and vaccines launched simultaneously in developing countries or intended for their exclusive use.⁴⁰ Some donor-funded global health programs conduct active surveillance to monitor adverse events following the introduction of a novel vaccine or drug, but their efforts are limited by a lack of background population data, and do not generally extend to routine surveillance or assessments of longer-term effects of those drugs and vaccines.

Targeted clinical trials and observational studies can be expensive, time-consuming, and complex – not a long-term solution for countries with very limited resources.⁴¹ Global health programs are also increasingly engaging developing country manufacturers to lower manufacturing costs and expand distribution.⁴² Generic companies provide a significant proportion of ARVs distributed in LMICs. These manufacturers are producing and distributing affordable, high quality drugs and vaccines pursuant to international standards, but may not have the resources, experience, or expertise to systematically monitor the safety of novel products post-market. The typical pharmacovigilance budget for multinational generic drug producers that supply most of the medicines in LMICs is a tiny fraction of the resources spent by multinational research-based biopharmaceutical firms.⁴³

Existing International Initiatives on Pharmacovigilance

A variety of initiatives seek to support and strengthen pharmacovigilance internationally. WHO defines, develops, and promotes guidelines, protocols and normative PV standards for use in LMICs. WHO, together with its collaborating centers in Accra, Oslo, Rabat, and Uppsala, coordinates international adverse event reporting from the more than 100 countries that participate in the WHO Program for International Drug Monitoring. The WHO collaborating center in Uppsala, the Uppsala Monitoring Centre (UMC), operates as an independent foundation and hosts the global ICSR database (Vigibase), which includes more than 8 million case reports; provides the WHO Drug Dictionary and the WHO Adverse Reaction Terminology (WHOART) to member

⁴⁰ Stephen Black, *Developing sustainable funding for vaccine safety infrastructure*, 28 VACCINE 133 (2010) (reporting that A whole cell DTP/Hib combination vaccine was released in South Asia but not elsewhere); Griffiths UK, Clark AD, Mulholland K. *Introduction of rotavirus vaccine*. 339 BMJ 3482 (2009) (noting GlaxoSmithKline introduced Rotarix, its rotavirus vaccine, in Mexico concurrently with its release in Europe).

⁴¹ SAFETY OF MEDICINES IN SUB-SAHARAN AFRICA, *supra* note 32.

⁴² For example, the commitment of the Serum Institute to provide the new meningitis vaccine at US\$0.40 per dose greatly enhanced the speed and breadth of the roll out of this new immunization program. PATH Meningitis Vaccine Project, Key facts on "MenAfriVac", the meningococcal A conjugate vaccine developed by MVP, available at <http://www.meningvax.org/files/MVP-FS-MenAfriVac.pdf>. See, e.g., Sarah E. Frew et al., *The Indian And Chinese Health Biotechnology Industries: Potential Champions Of Global Health?* 27 HEALTH AFF. 1029, 1030 (2008) (reporting that the Serum Institute of India has a 138-country global distribution network that provides one of every two doses of vaccines worldwide on behalf of United Nations Children's Fund (UNICEF) and Pan American Health Organization (PAHO) programs); Carlos M. Morel et al., *Health Innovation Networks to Help Developing Countries Address Neglected Diseases*, 309 SCIENCE 401 (2005) (describing the increasing engagement of emerging economy manufacturers in Brazil, Cuba, India, and Indonesia in global health treatment and immunization programs); WHO. 2010. New database for WHO prequalified vaccines, available at http://www.who.int/immunization_standards/vaccine_quality/PQ_vaccine_list_en/en/index.html (showing that a company in Senegal now manufactures and supplies yellow fever vaccines to GAVI and UN programs in other African countries).

⁴³ Lalvani and Milstien, *supra* note 30 (reporting that the annual PV budget for global pharmaceutical MNCs may range from \$5 million to \$20 million while the PV budget for generic MNCs may range between \$10,000 and \$100,000).

countries; licenses computer software for case report management (VigiFlow); and conducts data analysis, signal detection and methodological research in pharmacovigilance. Twenty-six percent of developing countries are registered members in the Program.⁴⁴ WHO also convenes the International Working Group on Drug Statistics Methodology, which provides the Anatomical Therapeutic and Chemical (ATC) classification of medicines and the Defined Daily Dose (DDD), which are two metrics that are important in studying global drug utilization.

The Advisory Committee on Safety of Medicinal Products (ACSoMP) and Global Advisory Committee for Vaccine Safety (GACVS) provide advice to the WHO Director-General (DG) and, through the DG, to WHO Member States on pharmacovigilance policy and issues related to the safety and effectiveness of medicinal products.⁴⁵ In 1949, WHO and the United Nations Educational, Scientific and Cultural Organization (UNESCO) established the Council for International Organizations of Medical Sciences (CIOMS), a nongovernmental organization that works closely with WHO to harmonize and strengthen drug safety surveillance measures by developing definitions of ADR terms and reporting formats. The Brighton Collaboration, a voluntary collaboration of professionals and organizations, and the CIOMS/WHO Working Group on Vaccine Pharmacovigilance develop standardized adverse event definitions and monitoring guidelines in connection with immunization.

In recent years, initiatives have been launched to improve post-market drug and vaccine safety in LMICs specifically. In 2007, WHO launched a European Commission (EC)-funded effort to support pharmacovigilance in selected African, Caribbean and Pacific Island countries.⁴⁶ In 2009, WHO launched the Global Network for Post-Marketing Surveillance of Newly Prequalified Vaccines in twelve LMICs to promote pharmacovigilance and sharing of adverse events reports.⁴⁷ That same year, with EC funding, WHO and UMC launched the Monitoring Medicines project to strengthen consumer safety reporting in developing countries, promote better and broader use of existing pharmacovigilance data, and develop active and focused surveillance methods.⁴⁸ In 2009, WHO established the WHO Collaborating Center for Advocacy and Training in Pharmacovigilance at the University of Ghana Medical School (WHO CC Ghana) to promote adoption of effective pharmacovigilance in Africa.⁴⁹ The Global Fund, WHO, and WHO CC Ghana also collaborated on the development of a global strategy and toolkit for a sustainable, global partnership for system-driven pharmacovigilance.⁵⁰ In 2011, USAID launched a five-year program on Systems for

⁴⁴ List of WHO International Drug Monitoring Program Members, available at <http://www.who-umc.org/DynPage.aspx?id=100653&mn1=7347&mn2=7252&mn3=7322&mn4=7442>.

⁴⁵ http://www.who.int/medicines/areas/quality_safety/safety_efficacy/pharmvigi/en;
http://www.who.int/immunization_safety/activities/en/.

⁴⁶ The EC-ACP-WHO Partnership,
http://www.who.int/medicines/areas/coordination/ecacpwho_partnership/en/index1.html

⁴⁷ http://www.who.int/immunization_safety/activities/en/

⁴⁸ World Health Organization, Recommendations from 8th meeting of the WHO Advisory committee on safety of Medicinal Products (ASCoMP) (2011); Monitoring Medicines, <http://www.monitoringmedicines.org>.

⁴⁹ <http://www.pvafrica.org>.

⁵⁰ Xueref S (2010) Towards a global strategy on pharmacovigilance. Presented at Global Surveillance of Antiretroviral Drug Safety meeting. June 11, 2010, Washington, DC. Available: <http://www>.

Improved Access to Pharmaceuticals and Services (SIAPS), which includes projects on strengthening pharmacovigilance in developing countries.⁵¹ A growing number of academic institutions are conducting collaborative pharmacovigilance activities, including training and research, with organizations within LMICs.⁵²

In 2011, the WHO Global Vaccine Safety Blueprint project developed a three-part strategy for promoting vaccine pharmacovigilance worldwide. This strategy includes establishing: (1) a minimum capacity for passive vaccine safety surveillance in all countries; (2) enhanced capacity for active surveillance in countries where newly developed vaccines will be introduced, or which will manufacture and/or use prequalified vaccines; and (3) a global support structure for training, collaboration, and information exchange.⁵³ In 2012, the World Health Assembly endorsed this strategy and WHO launched the Global Vaccine Safety Initiative to coordinate a portfolio of stakeholder-developed programs to implement the Blueprint.

Global health initiatives have incorporated pharmacovigilance objectives into their treatment and immunization programs, but funding has remained modest. Below are a few examples. GAVI has made limited funds available to establish national pharmacovigilance centers and training in South-East Asia.⁵⁴ In 2008, the Global Fund and Roll Back Malaria Partnership invited countries to incorporate pharmacovigilance objectives into their funding proposals.⁵⁵ The Bill & Melinda Gates Foundation sponsored two projects to improve post-market safety in HIV/AIDS programs in developing countries.⁵⁶

Finally, global health programs conduct active surveillance to monitor adverse events following the introduction of a novel vaccine or drug.⁵⁷ These efforts are limited, however, by a lack of background population data and do not generally extend to routine surveillance or assessments of longer-term effects of those drugs and vaccines.

hivforum.org/storage/hivforum/documents/PV2010/pharmacovigilance%20gf%20who%20concept%20note%20may%202010.pdf.

⁵¹ <http://www.msh.org/news-bureau/mshwins-five-year-cooperative-agreement-for-systems-for-improved-access-to-pharmaceuticals-and-services-program.cfm>. Its predecessor program, Strengthening Pharmaceutical Systems, also sought to strengthen pharmacovigilance in developing countries.

⁵² See SAFETY OF MEDICINES IN SUB-SAHARAN AFRICA, *supra* note 32, at 82.

⁵³ World Health Organization, Meeting of the Strategic Advisory Group of Experts on Immunization, November 2011 – Conclusions and Recommendations as found in the Weekly Epidemiological Record (Jan 6, 2012).

⁵⁴ World Health Organization, Adverse Events Following Immunization in the South-East Asia Region 2008-2010 (2011).

⁵⁵ <http://www.rollbackmalaria.org/mmss/docs/PharmacovigilanceIntro-en.pdf>

⁵⁶ Lalvani P, Milstein J. Access to new health products in low income countries and the challenges of pharmacovigilance. May 2011; Chris Duncombe, Priorities and Initiatives to advance pharmacovigilance in HIV program: presentation at WHO/GF stakeholder's meeting. Nov 2010, Accra, Ghana.

⁵⁷ See, for example, Maman. S. Chaibou et al., *Monitoring adverse events following immunization with a new conjugate vaccine against group A meningococcus in Niger, September 2010*, 30 Vaccine 5229 (2012); Claude-Roger Ouandaogo et al., *Adverse events following immunization during mass vaccination campaigns at the first introduction of a meningococcal A conjugate vaccine in Burkina Faso, 2010*, 30S Vaccine B46 (2012). Bompert F, Kiechel JR, Sebbag R. *Innovative public-private partnerships to maximize the delivery of anti-malarial medicines: lessons learned from the ASAQ Winthrop experience*. Malaria Journal 2011, 10:143.

A New Strategy

The foregoing sections of this report have outlined the reasons *why* stakeholders should invest in strengthening post-market safety surveillance in LMICs. Drugs and vaccines are now reaching unprecedented numbers of people in developing countries that lack capacity to effectively monitor the post-market safety of these products. Without timely and accurate information on safety and effectiveness, these products can unnecessarily harm patients and do lasting damage to the treatment and immunization programs. Despite the recent surge in international capacity building initiatives, progress on strengthening pharmacovigilance in LMICs remains largely elusive. Few LMICs have functional post-market safety systems and most do not yet report a robust number of suspected adverse events. With new donor funding scarce in this weak global economy, substantial new resources for addressing post-market safety needs may not be forthcoming. A new strategy is needed.

The remainder of this report is devoted to outlining the strategy that was developed to the Safety Surveillance Working Group (SSWG). It seeks to answer four questions.

First, this report addresses the question of *where* stakeholders should invest in strengthening post-market safety surveillance in LMICs. Given expanding post-market safety demands and scarce resources and infrastructure, prioritization is needed. This section proposes focusing on pharmacovigilance for the global health product pipeline in the near term and adopting a structured, risk-based approach to investing in post-market safety surveillance.

Second, this report addresses the question of *what* stakeholders should invest in to improve post-market safety in priority developing countries. This section makes the case for leveraging the pharmacovigilance conducted in support of new product introduction to build sustainable and functional post-market safety surveillance capacity in developing countries. Achieving this objective requires building LMIC pharmacovigilance programs that are affordable, durable, and capable of addressing the variety of priority post-market safety concerns.

Third, this report examines the question of *how* stakeholders should invest in strengthening post-market safety surveillance in LMICs. While prioritization is necessary in the near term, investments in post-market safety surveillance programs should be designed to be scalable to the broader needs of LMICs.

Last, this report considers the question of *who* – which stakeholders must invest in order to move this strategy toward implementation. It ends with a call and plan for action in the near term.

The strategy set forth in this report is meant to complement and build upon, not duplicate or replace, existing international pharmacovigilance capacity building initiatives, WHO technical assistance programs, and disease- and product-specific initiatives. The human and financial resources available to strengthen post-market safety surveillance in developing countries are already limited. Progress can only occur if synergies between initiatives are encouraged and reinforced.

Where to Invest

Given expanding needs and scarce resources, investments in strengthening LMIC pharmacovigilance programs must be prioritized. International initiatives supporting post-market safety surveillance in LMICs should prioritize the demands of the global health product pipeline in the near term. The global health pipeline includes the novel and newly introduced drugs and vaccines that may be distributed through global health programs, such as GAVI and Global Fund, for use in resource-poor populations internationally for HIV/AIDS, malaria, TB, cervical cancer, family planning, and the dozen other parasitic, soil transmitted, bacterial, and tropical infections that are defined as ‘neglected diseases.’ The reasons for focusing on this pipeline are threefold.

First, developing country regulators will not be able to rely on the safety assessment conducted in developed countries for these novel or newly introduced drugs and vaccines since most will be launched exclusively or simultaneously in LMICs. Accordingly, it is essential to establish sufficiently robust post-market safety surveillance to enable, at a minimum, the timely identification and evaluation of events that are sufficiently frequent and significant to potentially justify a change in the registration status or approved indications of those products. This focus on this product pipeline is further justified because the countries most heavily engaged in these global health programs tend to be the poorest and have the most limited post-market safety surveillance systems.

Second, post-market safety needs for the candidate drugs and vaccines in the global health pipeline are relatively predictable and quantifiable because data exist on their projected distribution. These data allow preemptive action to ensure adequate oversight exists in these countries and patient populations.

Third, global health programs offer potential partnerships, resources, and expertise that may be leveraged to build sustainable and capable pharmacovigilance systems in LMICs. The entities involved in the global health product development projects – multilateral development banks, aid agencies, philanthropic foundations, technical and procurement institutions, PDPs, academic institutions, and multinational pharmaceutical firms – have resources, expertise, and clout needed to help prioritize and improve pharmacovigilance in LMICs.

Even with a focus on post-market safety demands of the global health product pipeline, however, further prioritization will be needed. Global health programs are projected to introduce dozens of potentially lifesaving drugs and vaccines into a significant number of LMICs over the next decade. Investments in post-market safety surveillance should reflect a risk-based assessment of LMIC needs and dedicate resources to those approaches most likely to satisfy priority demands given local infrastructure constraints.

This chapter proposes risk-based criteria for assessing developing country needs for post-market safety surveillance and applies that proposed criteria to the data available regarding the current global health product pipeline. This analysis represents a snapshot in time, based on the best data

available; its projections are likely to change as candidate products advance through clinical development and new and more complete data emerge. This preliminary analysis is included here to illustrate risk-based prioritization is possible and could be used to deploy the available funds and technical resources in a targeted manner in order to achieve their greatest impact for LMICs.

Risk-based Criteria

The proposed risk-based prioritization of post-market safety surveillance needs is based on the following criteria:

1. A determination, based on the best information available, the drugs and vaccines that are expected to be introduced in LMICs over the next ten years and the countries where these products will be introduced;
2. An assessment, based on the best information available, of the anticipated and potential post-market safety risks of those drugs and vaccines to patients;
3. A determination of the timeframe when the product will be launched in the country at issue; and
4. An assessment of the current capacity of the launch country to support post-market safety surveillance of high-risk products.

The anticipated product pipeline.

For reasons already outlined above, this analysis focuses on the global health product pipeline, not all drugs and vaccines to be introduced in developing countries over the next decade. The percentage of the overall volume of drugs and vaccines that this pipeline represents will vary across LMICs, but is likely to be greater in poorer countries and will diminish over time as drug sales to LMICs increase. These data represent all known products in the global health product pipeline, not just those that are Bill and Melinda Gates Foundation-supported. Most of the data represents product launches that will be donor-supported, usually through GAVI or the Global Fund, and accordingly may not include countries where introduction of the same drugs and vaccines will occur without such support. The authors limited their analysis to candidate drugs and vaccines that are currently in phase II or higher; projections based on earlier stage candidates are unlikely to be reliable. Accordingly, fewer launches are indicated for the long-term periods assessed in this analysis.

The primary sources of the pipeline data are Bill and Melinda Gates Foundation staff, a Boston Consulting Group global health product pipeline analysis, and publications concerning the candidate products. The data are more complete for vaccines than drugs, particularly with regard to anticipated launch countries. In order to ensure a robust representation of drug and vaccine candidates in the proceeding analysis, the authors assumed, where no other information was available, that the LMICs where the late-stage clinical trials (phase II b or higher) occurred for a candidate drug or vaccine occurred will also be the countries where that product will be introduced. This assumption was only applied in a few cases, but may not always be correct and is likely to underestimate the number of countries in which those products will be launched.

The anticipated and potential post-market safety risk.

The authors propose that post-market safety product risk be assessed on four criteria.

First, the risk of a drug or vaccine to patients should depend on the frequency and the severity of the adverse effects of the medical product. This includes known as well as potential risks that will require further evaluation. This criterion is commonly used in risk assessment by stringent regulatory authorities when considering the benefit-risk of a medical product. In evaluating these risks, particular emphasis should be placed on interpretation of data related to newly identified safety concerns or providing significant new information on previously identified safety concerns. Safety signals that emerge from drug development that may warrant special attention in pharmacovigilance planning are suggested in the annex of this report (Table 4). Risk-based safety surveillance places special emphasis on identified safety issues, allowing investments to be prioritized in the development and implementation of pharmacovigilance and benefit-risk management plans.

Second, risk depends on the type of product and its anticipated use. The risks of post-market harm are higher for vaccines and drugs provided presumptively and prophylactically to otherwise healthy individuals, often children. Donors, sponsors, and local governments have a greater obligation to protect from unnecessary harm the patients who voluntarily participate in immunization and mass treatment programs. Immunization programs are often introduced en masse and, thus, expose large numbers of patients to the product in a short period of time. Live attenuated vaccines may elicit a mild form of the disease, or, in rare instances, a full-blown case. If unaddressed, real or rumored adverse events involving vaccines and drugs provided presumptively and prophylactically can undermine public confidence, and do lasting damage to treatment and immunization programs.

Third, risk depends on novelty.⁵⁸ Much remains unknown about a novel drug or vaccine upon registration. Some of the candidate drugs and vaccines in the global health pipeline are based on novel technologies with limited history of human use. There may be only limited clinical data involving that product in the target country or similar settings. In some instances, the drug or vaccine may have been granted accelerated review and lack a full profile of research. The need for adequate post-market safety surveillance of such products is particularly critical. Conversely, the priority of post-market safety surveillance may be lower for a drug or vaccine that employs a similar mechanism of action as a product already on the market with a favorable benefit-risk profile in the target setting.

Fourth, the anticipated and potential risk of a product depends on the subpopulations that may be exposed. Clinical trials often exclude vulnerable patients, such as pregnant women, individuals with co-morbidities, and patients taking other medications. These patients are often more vulnerable to adverse health events and the potential risks of such events occurring are uncertain. The use of new

⁵⁸ Since November 2005, risk management plans must be submitted as part of marketing applications for all NCEs in the EU. Stringent regulatory authorities establish specific intervals for reviewing all accumulated safety information on NCEs for a defined period following approval.

medical products by pregnant women in particular is not uncommon – inadvertent and intentional exposures occur.⁵⁹ Passive surveillance of adverse pregnancy outcomes is often insufficient.⁶⁰

Existing pharmacovigilance capacity in the projected launch countries

Numerous assessments exist of post-market safety surveillance capacity in LMICs. WHO has conducted studies of the regulatory capacity in LMIC governments, which include assessments of pharmacovigilance.⁶¹ FDA and USAID are working with Management Sciences for Health to assess the pharmacovigilance capacity of selected countries in sub-Saharan Africa and Asia.⁶² In 2010, the Global Medicines Program of the University of Washington⁶³ and WHO conducted a Bill and Melinda Gates Foundation-funded analysis of the pharmacovigilance capacity of 55 LMICs.⁶⁴ These assessments are not exhaustive or comprehensive, but provide a preliminary basis for determining the current pharmacovigilance capacity in the countries in which global health initiatives will launch novel and newly introduced vaccines and drugs over the next decade. For countries for which no public information exists concerning their pharmacovigilance capacity, the authors used membership in the WHO International Drug Monitoring Program and the number of reports that the country contributed to the WHO global ICSR database (Vigibase) as rough proxies for pharmacovigilance capacity.

Timing

The final consideration for prioritization is timing. All else equal, the need for post-market safety surveillance is more urgent for products that will be introduced sooner in LMICs.

Application

To conduct this assessment, the Bill and Melinda Gates Foundation and its partners shared information on the content of the global product development pipeline by product name, stage of development, and current projections on the timing and target countries for product introduction.

⁵⁹ White NJ, McGready RM, Nosten FH. *New medicines for tropical diseases in pregnancy: catch-22*. PLoS Med. 2008 Jun 17;5(6):e133.

⁶⁰ The US FDA and the EU, for example, recommend active surveillance for products that are likely to be used during pregnancy or by women of childbearing age, particularly if there have been case reports of adverse pregnancy outcome following exposure, drugs in the same pharmacological class are known to pose risk during pregnancy or pre-clinical animal data suggest potential teratogenic risk. FDA Center for Drug Evaluation and Research & Center for Biologics Evaluation and Research, Guidance for Industry: Establishing Pregnancy Exposure Registries (2002); European Medicine Agency, Guideline on the exposure to medicinal products during pregnancy: need for post-authorisation data. (2005).

⁶¹ See, e.g., WORLD HEALTH ORGANIZATION, ASSESSMENT OF MEDICINES REGULATORY SYSTEMS IN SUB-SAHARAN AFRICAN COUNTRIES: AN OVERVIEW OF FINDINGS FROM 26 ASSESSMENT REPORTS (2010).

⁶² Safety of Medicines in Sub-Saharan Africa, *supra* note 32; Preliminary Findings from Assessment of Pharmacovigilance Systems in SE Asian Countries, Submitted to USAID by SIAPS, 2012 (on file with authors).

⁶³ www.globalmedicines.org

⁶⁴ Olsson et. al., *supra* note 29.

A literature search was then conducted for those products in phase II, III, awaiting regulatory approval, or post-launch to identify potential safety risks by type of potential safety concern, frequency, and a qualitative severity rating. For vaccines, the literature included safety reviews from the WHO Strategic Advisory Group of Experts (SAGE) on Immunization, where available.

Three rankings of risk were used: low, medium, and high. These rankings are defined as follows.

- **Low:** Product has considerable post-marketing experience and data from safety surveillance demonstrate little to no risk of serious adverse events.
- **Medium:** Product has important potential risks, identified risks or important missing information. By definition, products presently in Phase II of development fall into this category due to the insufficient knowledge of product safety as an inherent limitation of early clinical studies.
- **High:** Product has important potential risks, identified risks or important missing information, and pharmacovigilance beyond routine pharmacovigilance has been requested or is likely to be requested during the approval process.

These product risk rankings are relative, not absolute, and are not intended to suggest that a particular candidate drug or vaccine is unsafe upon introduction. These rankings are intended to help prioritize scarce post-market safety surveillance resources to support the countries and product launches that most require that support. Examples of product descriptions and risk rankings appear in the annex to this report.

This analysis also assesses the relative pharmacovigilance capacity of the countries expected to host the greatest number of higher risk product over the next decade. Three rankings of relative capacity were used:

- **Least Capacity:** The country is either not a member of the WHO International Drug Monitoring Program, only an associate member, or joined the Program in the last two years. In most cases, the SIAPS Program or another credible source has also assessed the country to have no or minimal pharmacovigilance capacity.
- **Midrange Capacity:** The country has been a member of the WHO International Drug Monitoring Program for two or more years. In most cases, the SIAPS Program or another credible source has assessed the country to have some modest pharmacovigilance capacity, although its rate of reporting of ADRs to the WHO database may be low.
- **Most Capacity:** The country has been a member of the WHO International Drug Monitoring Program for five or more years. In most cases, the SIAPS Program or another credible source has also assessed the country to have a pharmacovigilance system capable of detecting, evaluating, and preventing medicine safety issues.

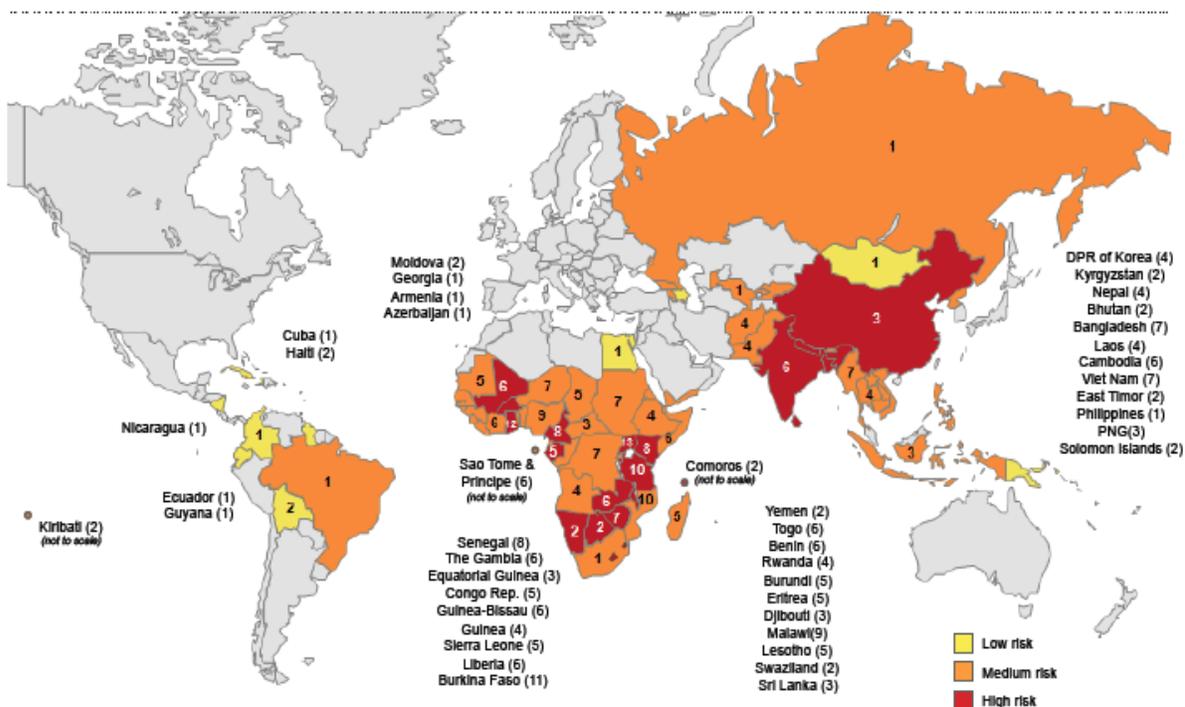
As with the product risk rankings, these capacity rankings are relative, not absolute. The rankings are not intended to suggest that the countries assessed have sufficient pharmacovigilance capacity and do not require capacity building. Tables 1-3 in the annex provide the full list of the countries assessed and the justifications for their ranking.

Results

Figures 1, 3, and 5 below depict the countries that are expected to host product launches in the short term (2012-2015), medium term (2016-2018), and long-term (2019-2022). These figures indicate the number of novel or newly introduced product launches each country is projected to host in that time period. The colors – yellow (lower risk), orange (medium risk), and red (higher risk) – reflect the highest risk product that country is projected to host during that time period.

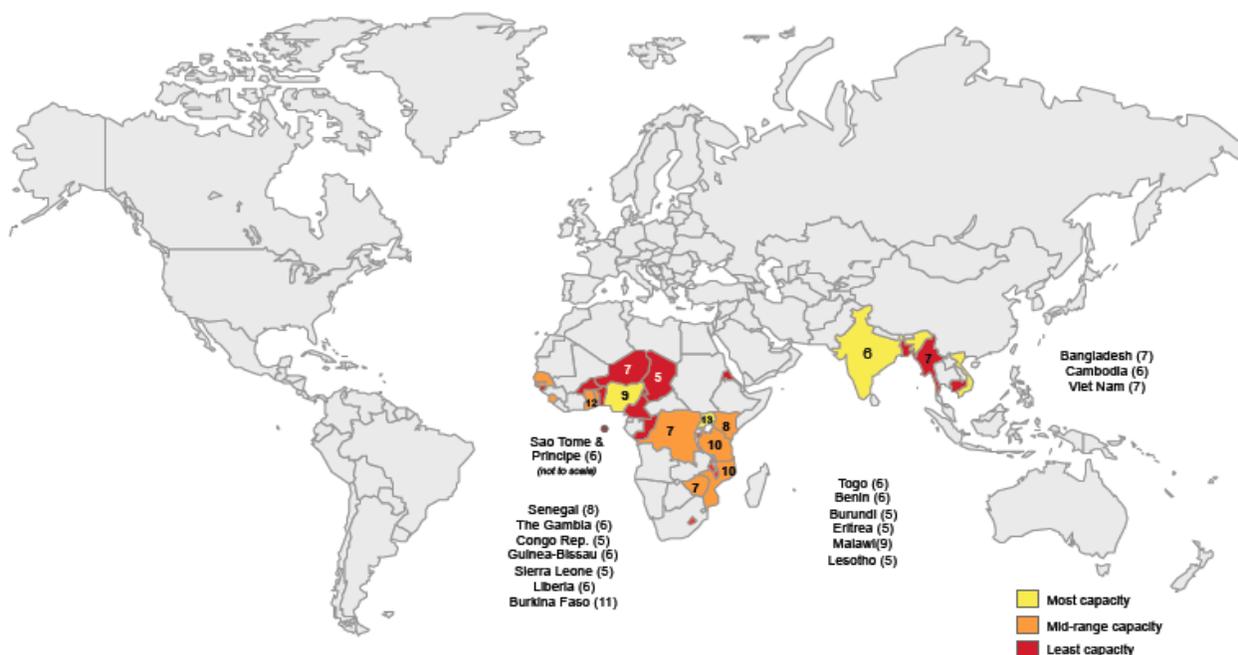
Figures 2, 4, and 6 below depict the relative pharmacovigilance capacity of the countries that are projected to host the greatest number of higher-risk product launches in the short term (2012-2015), medium term (2016-2018), and long-term (2019-2022). The colors – yellow (most capacity), orange (midrange capacity), and red (least capacity) – reflect the relative pharmacovigilance capacity of that country. These figures also indicate the number of product launches each country is projected to host during that time period.

Figure 1:
Geographic distribution of product launches, assessed by relative risk (2012-2015)



In the **short term** (2012-2015), three clusters are apparent in which all countries are projected to host seven or more product introductions, at least one of which that the authors have rated medium risk or higher. In West Africa, Benin, Burkina Faso, Cameroon, Ghana, Niger, Nigeria, and Senegal are all projected to host seven or more such product introductions. In East and Southern Africa, the Democratic Republic of Congo, Kenya, Malawi, Mozambique, Tanzania, Uganda, and Zimbabwe are projected to meet these criteria.⁶⁵ In South Asia, Bangladesh and India fit this group. In South-east Asia, Myanmar and Viet Nam are projected to have seven or more such product launches and Cambodia will have six. In the short term, East and West Africa and South Asia are projected to host to the greater numbers of higher-risk product launches.

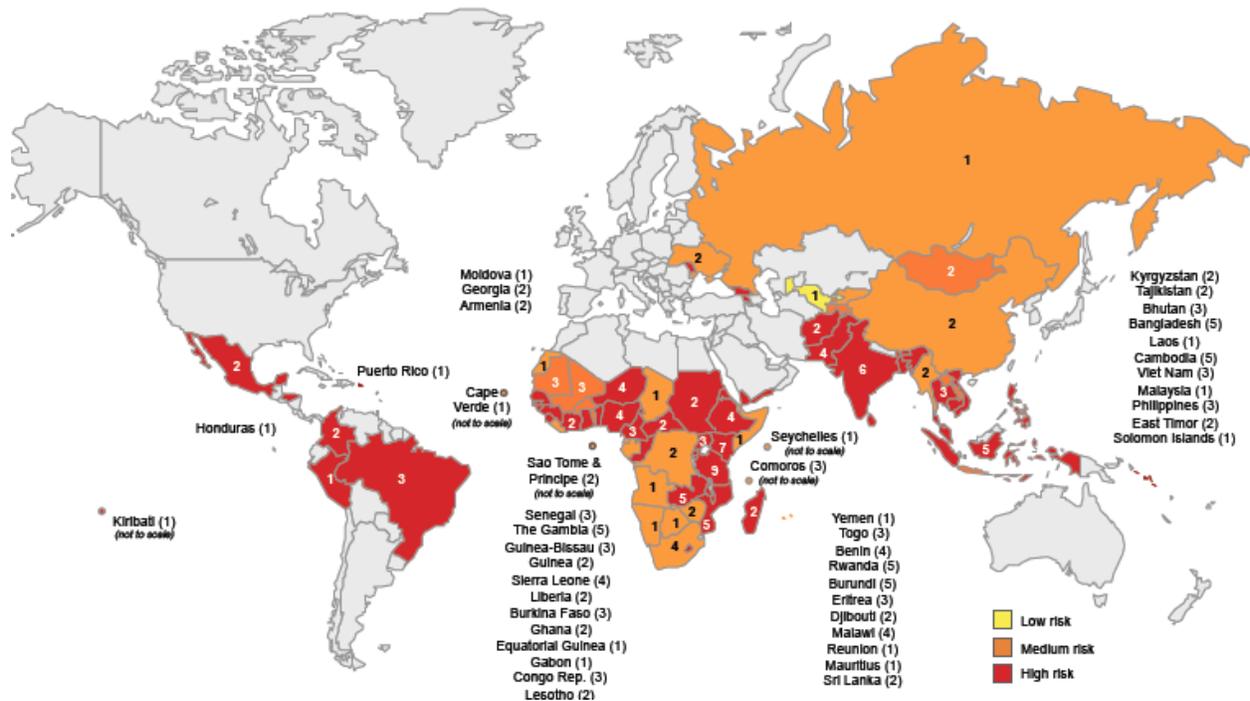
Figure 2: Relative pharmacovigilance capacity of countries projected to host five or more higher-risk product launches (2012-2015)



Several of the countries that will host the introduction of five or more higher-risk products in the short term (2012-2015) have no capacity to ensure post-market safety surveillance of these products. Most of these countries are in West Africa – Benin, Burkina Faso, Cameroon, Chad, the Congo Republic, Guinea Bissau, Niger, and São Tomé & Príncipe. Bangladesh will also host a significant number of higher-risk products with little pharmacovigilance capacity to support those introductions. A cluster of countries in East Africa will host the greatest number of higher-risk product introductions and have only minimal or modest structures in place to support their post-market safety surveillance.

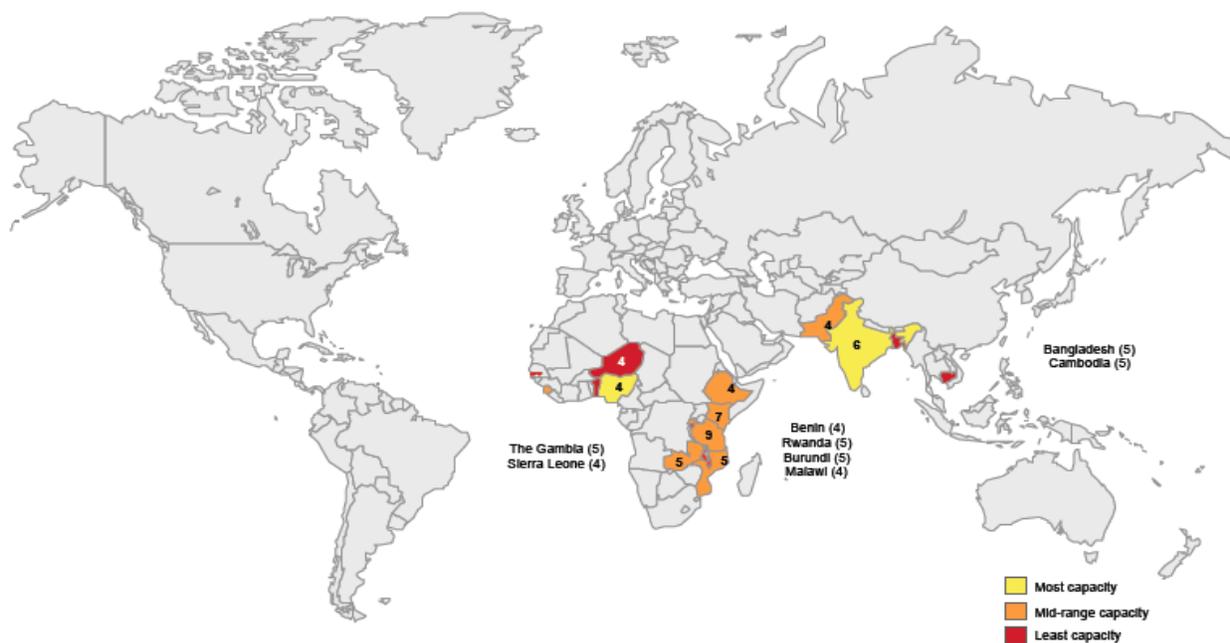
⁶⁵ Please note the mapping software used for the figures in this report has not yet been updated to reflect the independence of South Sudan so that the figures in this paper reflect the product launches that are expected to occur in both South Sudan and North Sudan, which leads to some double counting.

Figure 3:
Geographic distribution of product launches, assessed by relative risk (2016-2018)



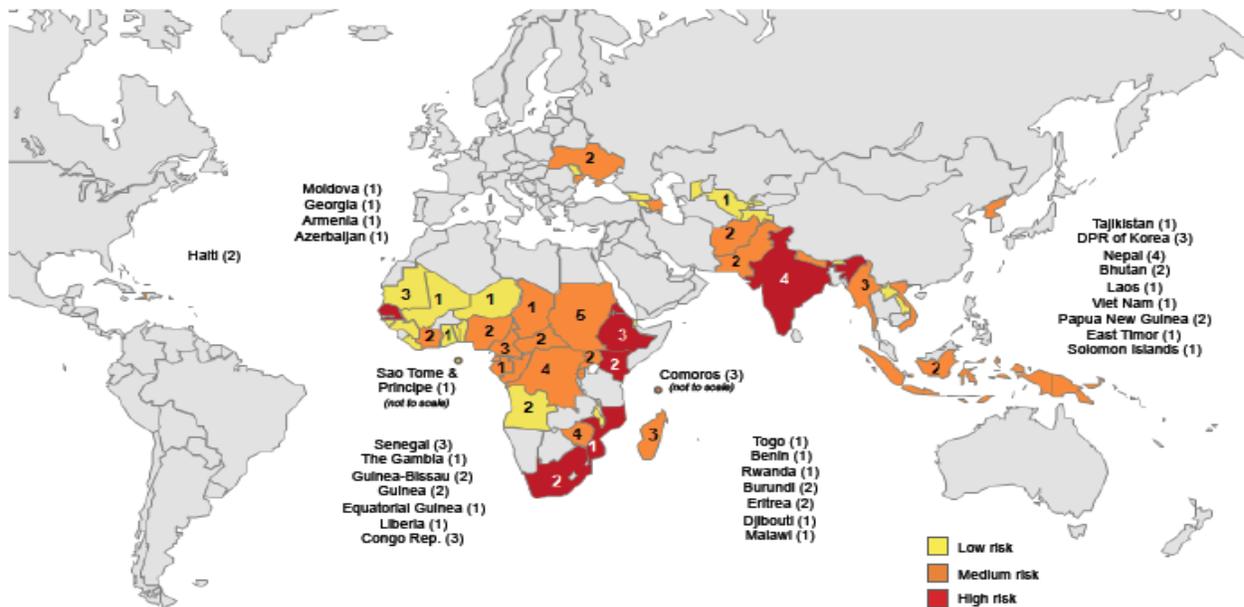
In the **medium term** (2016-2018), regional clustering again occurs. In East Africa, Kenya, Mozambique, and Tanzania are again projected to host five or more higher risk product launches, as are Burundi, Rwanda, and Zambia. In West Africa, Benin, The Gambia, Niger, and Nigeria are expected again to have four or more higher-risk product launches. In South Asia, Bangladesh, India, and Pakistan have four or more higher-risk product launches as well. There is less regional clustering in South-east Asia, but Cambodia and Indonesia are each expected to see five or more such product launches. Latin America is projected to see fewer product launches according to the current data, but these launches will be higher risk

Figure 4: Relative pharmacovigilance capacity of countries projected to host four or more higher-risk product launches (2016-2018)



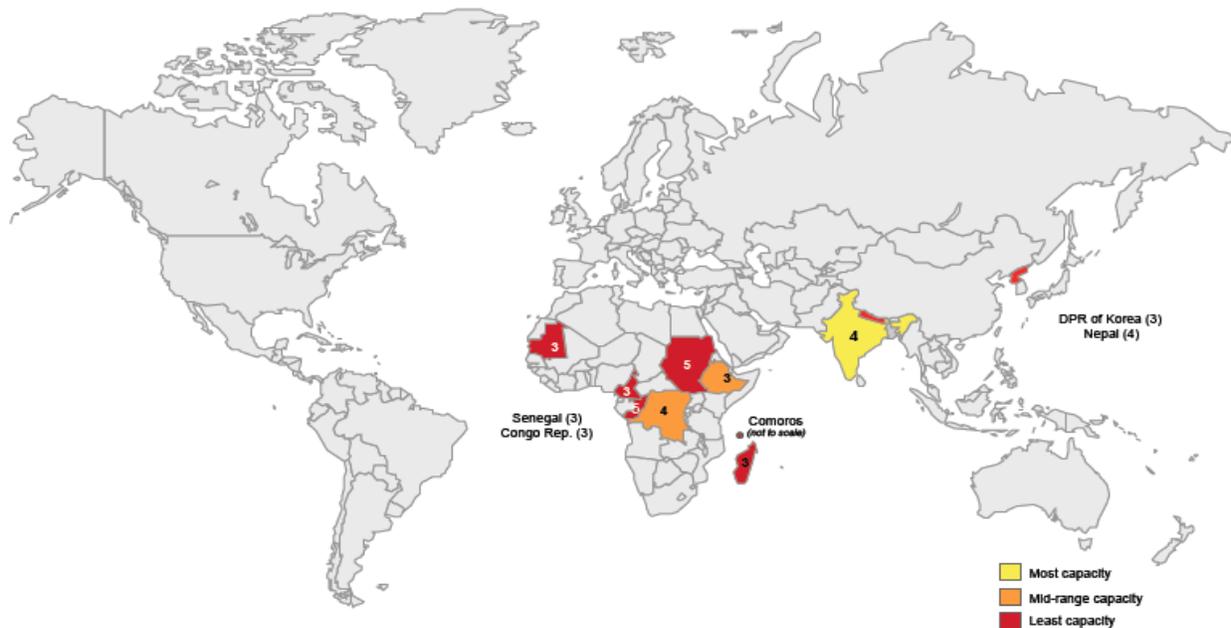
Several countries will host the introduction of four or more higher-risk products in the medium term (2016-2018) with no capacity to ensure post-market safety surveillance of these products. Most of these countries are the same as those that are projected to host a high number of such introductions in the short term: Bangladesh, Benin, Burundi, Cambodia, and Niger. A cluster of countries in East Africa will host many higher-risk product introductions with only minimal or modest structures in place to support their post-market safety surveillance.

Figure 5:
Geographic distribution of product launches, assessed by relative risk (2019-2022)



In the **longer-term** (2019-2022), data on projected product launches is less robust and likely to be less reliable. The data currently available suggests that East Africa and South Asia are expected to host again the greatest number of higher risk product launches, Ethiopia and India in particular. Bangladesh, the Democratic Republic of Congo, and Madagascar are also projected to see increased activity during this time period.

Figure 6: Relative pharmacovigilance capacity of countries projected to host three or more higher-risk product launches (2019-2022)



Projections regarding the long-term capacity of countries to host higher-risk product introductions are also likely to be less reliable, as pharmacovigilance may well improve in some or all of these settings by 2019. Most of the countries projected to host three or more higher-risk product introductions with no or little current pharmacovigilance capacity are in East and West Africa: Cameroon, Comoros, Congo Republic, Democratic Republic of Congo, Ethiopia, and North and South Sudan.

Observations

Five important observations may be made regarding the findings of this risk-based analysis.

First, the data currently available suggests that the following countries will host the greatest number of higher risk product launches over the ten-year period assessed: Bangladesh, Benin, Ghana, India, Kenya, Mozambique, Nigeria, Senegal, Tanzania, and Uganda. A disproportionate number of such launches will occur in the East Africa and South Asia regions.

Second, only four of the nearly two dozen LMICs that are projected to host ten or more higher-risk product introductions before 2022 have performing pharmacovigilance systems: India, Nigeria, Uganda, and Vietnam.

Third, independent assessments of most of the remaining countries indicate the presence of some minimal pharmacovigilance structures that may be leveraged to support product introduction and

longer term capacity building efforts.⁶⁶ According to recent analyses, the Democratic Republic of Congo, Ethiopia, Ghana, Kenya, Mozambique, Rwanda, Senegal, Tanzania, Zambia, and Zimbabwe all have some basic or modest basic or modest pharmacovigilance capacity.⁶⁷ Building post-market safety surveillance in such settings is feasible.

Fourth, the iterative nature of the product introductions in these settings suggest the need to leverage the pharmacovigilance campaigns conducted in support of these novel or newly introduced drugs and vaccines to build sustainable post-market safety surveillance systems in these countries. Each new product introduction should not be forced to establish supporting pharmacovigilance infrastructure anew, but rather build on the investments of past introductions.

Fifth, the regional orientation of projected product launches and capacity-building demands suggests the possibility of regional and cooperative approaches to supporting the post-market safety surveillance needs of LMICs.

Limitations

Only those drugs or vaccines that were identified in the information obtained from the Bill and Melinda Gates Foundation were included in this analysis. Further, the scope of this analysis does not include products that are either preclinical or in Phase I due to the paucity of experience in humans. Specific drug and vaccine product risk assessments are based on information available in the public domain as of the time of this report. Risk assessment profiles should be living documents, periodically reviewed to incorporate additional data throughout the product lifecycle as the generation of new information has the potential for altering benefit-risk profiles.

This risk-based assessment did not incorporate an estimate of the number of patients that will likely be exposed to each candidate product in the pipeline, which would have improved the rigor of the analysis. Accurately forecasting the effective demand and likely uptake of a novel or newly introduced drug or vaccine is a long-standing challenge for many global health initiatives;⁶⁸ conducting that analysis for the dozens of candidate products in the global product pipeline was beyond the scope of this project, given its staffing and abbreviated time frame. Future assessments of LMIC post-market safety surveillance needs should incorporate patient exposure estimates.

This analysis also did not include evaluations of the efficacy or effectiveness of the drugs or vaccines in the pipeline, which is an important component of benefit-risk evaluations. Ensuring adequate post-market safety surveillance is not only about monitoring risk. New evidence on the benefits of a drug or vaccine continues to emerge over that product's lifecycle and can have important consequences for the use of that product and patient outcomes. Appropriate benefit-risk assessments can provide useful information for improved regulatory decision-making, helping to

⁶⁶ SAFETY OF MEDICINES IN SUB-SAHARAN AFRICA, *supra* note 32.

⁶⁷ *Ibid.*

⁶⁸ Center for Global Development, A Risky Business: Saving money and improving global health through better demand forecasts 64-67 (2007).

balance population-level risks and benefits.⁶⁹ Accordingly, stringent regulatory authorities are increasingly requiring benefit-risk assessments throughout the life cycle of a pharmaceutical product.⁷⁰

Last, this analysis has not involved an independent and comprehensive assessment of LMIC pharmacovigilance capacity and performance, which may limit its accuracy. A fully accurate assessment of a country's pharmacovigilance program requires field visits, interviews, and extensive independent investigation, which were beyond the scope of the SSWG. WHO has reportedly conducted independent assessments of its Member States' pharmacovigilance capacity, but is unable to share country-specific information because it does not have the permission of those Member States to do so. Accordingly, this report's analysis relies on the available, credible capacity assessments that USAID and MSH recently conducted, with the support of the U.S. FDA, of LMICs in Africa and South Asia and other proxies for capacity including membership in the WHO International Drug Monitoring Program and the number of reports that a country has contributed to the WHO global ICSR database (Vigibase). These capacity measures are undoubtedly imperfect, but the authors have ensured that the relative capacity rankings included in this report are all based on multiple data sources and, thus, corroborated to the greatest extent feasible.

⁶⁹ Guo JJ, Pandey S, Doyle J. A review of quantitative risk-benefit methodologies for assessing drug safety and efficacy-report of the ISPOR risk-benefit management working group. *Value Health*. 2010 Aug;13(5):657-66

⁷⁰ Section 909, Food Drug Administration Amendments Act of 2007. Available from: <http://www.fda.gov/offcampus.lib.washington.edu/oc/initiatives/HR3580.pdf>; E2C(R2) Periodic Benefit-Risk Report. ICH. 2012. <http://www.ich.org/products/guidelines/efficacy/efficacy-single/article/periodic-benefit-risk-evaluation-report.html>.

What to Invest In

The focus of most international pharmacovigilance capacity building efforts to date has been establishing a minimum capacity in all countries to conduct passive safety surveillance and, as competence improves, enhancing that capacity to implement active surveillance. This approach is considered international best practice and has helped to introduce pharmacovigilance concepts into LMICs, promote the use of consistent terminology and methodology, and establish national points of contact for pharmacovigilance. This approach, however, has two significant shortcomings as the exclusive strategy for addressing the pharmacovigilance challenges that currently face many LMICs.

First, this approach has enjoyed only limited success to date in attracting the investment of political capital and resources from participating governments and the support of the relevant industry, health professionals, and patient stakeholders. LMIC governments face a multitude of serious public health demands and historically have not prioritized investments in regulatory systems in general, and post-market safety surveillance in particular. A recent analysis of 55 LMICs found that fewer than half of the countries had a budget for pharmacovigilance activities.⁷¹ Adverse event reporting rates remain extremely low in most developing countries.

Second, this current approach is ill suited to help identify post-market safety risks of novel and newly introduced drugs and vaccines, particularly in LMICs. Passive safety surveillance relies on voluntary reporting from patients and health professionals, which is generally low in LMICs due to poor infrastructure and insufficient human resources.⁷² In many countries, medical professionals have no legal obligation to report adverse events and may fear reprisals if they do. Poor quality reports, insufficient training for reviewers, and lack of data on population background rates prevent the assessment of the causality of serious adverse events that do emerge through passive safety surveillance. Recent pharmacovigilance campaigns conducted in support of the introduction of the Meningitis A vaccine in Mali and Burkina Faso revealed that active surveillance generated significantly more adverse events than the countries' passive surveillance systems.⁷³

Recent research by Lant Pritchett, the well-regarded Professor of International Development at Harvard, on “capability traps” may be instructive here.⁷⁴ According to Pritchett, aid initiatives seeking to build the capabilities of human systems like education ministries, militaries, and regulatory agencies often fail because these initiatives promote the adoption of laws, administrative processes, and organizational practices that accord with international best practices, but do not reflect the

⁷¹ Olsson et. al., *supra* note 29.

⁷² Graham JE, Borda-Rodriguez A, Huzair F, et al. *Capacity for a global vaccine safety system: The perspective of national regulatory authorities*. *Vaccine*. 2012; 30:4953– 4959.

⁷³ See Maman. S. Chaibou et al., Monitoring adverse events following immunization with a new conjugate vaccine against group A meningococcus in Niger, September 2010, 30 *Vaccine* 5229 (2012); Claude-Roger Ouandaogo et al., Adverse events following immunization during mass vaccination campaigns at the first introduction of a meningococcal A conjugate vaccine in Burkina Faso, 2010, 30S *Vaccine* B46 (2012).

⁷⁴ Lant Pritchett, Matt Andrews, and Michael Woolcock, *Escaping Capability Traps through Problem-Driven Iterative Adaptation*, Center for Global Development Working Paper 299 (2012).

particular country's needs or capabilities. Accordingly, the resulting policy reforms are not implemented or used. Despite poor performance of the reform, donors and international technical agencies continue to support and recognize the government for adopting international best practice, further undermining the impetus for effective action. The government's capability stagnates or deteriorates even though it may continue to participate in the international aid initiative. Pritchett's prescriptions for escaping such capability traps include engaging an inclusive range of local stakeholders in the design of solutions to ensure they are politically supportable and practically implementable, and adapting those solutions as evidence emerges concerning their performance.

Three insights emerge from Pritchett's analysis. First, pharmacovigilance capacity building initiatives cannot achieve sustained improvements in performance by investing in what effective pharmacovigilance programs and institutions *look like* elsewhere, rather than what they will need to *do* in the setting in which these programs and institutions are employed. Accordingly, initiatives to improve pharmacovigilance capacity should be developed in cooperation with local governments and reflect local priorities and capabilities; incorporate the input of industry, health professionals, patient groups (where they exist), and other stakeholders to ensure initiatives' viability and relevance; and adjusted on an ongoing basis to respond to emerging evidence regarding performance.

Second, pharmacovigilance initiatives must be designed from the outset to generate industry and local government buy-in into these systems. As an operational matter, effective risk identification, assessment, mitigation, and communication requires the commitment and cooperation of local regulators, health professionals, public health officials, and industry stakeholders to succeed. As a funding matter, donor investments in improving pharmacovigilance capacity in LMICs will be limited in duration and amount. The sustainability of these systems will depend on developing country governments committing political capital to their pharmacovigilance programs and working with industry to ensure these programs are sufficiently resourced.

Third, pharmacovigilance initiatives must be designed to stretch the limited resources and be able to address as many priority post-market safety needs as possible. The need for increased support for post-market safety surveillance in LMICs may seem bottomless, but the resources available to meet that need are not. Donor and governments' investment in regulatory capacity has historically lagged behind most other areas of public health. Local governments are more likely to support post-market safety if it is feasible within the constraints of local resources and capabilities.

With these insights in mind, this report recommends the five-prong strategy below for strengthening the post-market safety surveillance, as a complement to the approach existing international pharmacovigilance capacity building initiatives.

Leverage Medical Product Introduction

This report recommends inverting the traditional capacity building paradigm by leveraging the pharmacovigilance conducted in support of the distribution of novel or newly introduced drugs and vaccines to catalyze and build sustainable and broadly functional post-market safety surveillance

systems. Many of the most successful examples of health systems building have occurred in service of delivering a particular treatment or other health intervention. For example, the dramatic scale-up of HIV/AIDS treatment in lower-income countries through the PEPFAR program facilitated the development of service delivery platforms that are now being used to support the delivery of health interventions for other diseases.⁷⁵

Similarly, the pharmacovigilance campaigns conducted in support of the distribution of novel or newly introduced products provide critical opportunities to improve post-market safety surveillance in priority settings.⁷⁶ As the risk-based analysis in the previous section of this report demonstrated, many countries, particularly in South Asia and East and West Africa, will be hosting multiple higher-risk drug and vaccine introductions in the next decade, often with the support of the same few donors and treatment and immunization programs. These introductions offer the chance to train and collaborate with local authorities in the context of addressing a public health challenge, instead of attempting to train and establish technical programs in the abstract. Promoting sustainable local capacity and internationally consistent approaches would improve the long-term surveillance of the drug or vaccine at issue and reduce the investment required for future product introductions.

Some of the strategies that may be incorporated into new product introduction to build sustainable post-market safety surveillance are outlined below. The example of the Japanese Encephalitis vaccine introduction in India, described below, highlights many of these strategies.⁷⁷

⁷⁵ See, e.g., Miriam Rabkin and Wafaa M. El-Sadr, *Why reinvent the wheel? Leveraging the lessons of HIV scale-up to confront non-communicable diseases*, 6 GLOBAL HEALTH 247 (2011).

⁷⁶ See also Jean-Michel Tassie, Silvia Bertagnolio and Yves Souteyrand. Integrated surveillance of HIV care in low-income and middle-income countries. *Current Opinion in HIV and AIDS* 2011,6:233–238 (authors with the WHO Department of HIV/AIDS advocating that the global scale-up of ART should be accompanied by robust programmatic assessment of the whole spectrum of HIV care components, including pharmacovigilance).

⁷⁷ See PATH, *Japanese Encephalitis Vaccine Introduction in India: Key Lessons Learned* (Nov. 2006) for more details on this pharmacovigilance program.

Introduction of the Japanese Encephalitis Vaccine in India

The pharmacovigilance campaign conducted in support of the introduction of a live-attenuated Japanese Encephalitis (JE) vaccine in India in 2006 provides a good example of the strategies proposed in this report. India had not been an early adopter of vaccines and had never undertaken an injectable vaccination campaign. Chengdu Institute of Biological Products, a Chinese firm, manufactured the JE vaccine, which concerned some Indian health officials. The vaccination campaign occurred primarily among the rural poor. At the time, India had no functional pharmacovigilance system.

The pharmacovigilance campaign is described in detail elsewhere, but some of its important lessons are as follows. First, PATH, the PDP involved, engaged the India Ministry of Health and Family Welfare (MHOFW) in the design, planning, and implementation of the pharmacovigilance campaign. Second, the pharmacovigilance campaign leveraged existing infrastructure – adapting an existing training module and operational guide and local health officials – to conduct the campaign. Third, the Government of India invested in key, sustainable infrastructure – fax machines and dedicated phone lines to facilitate communication and reporting between district and central health officials – and PATH trained rapid response teams of local officials to respond to cases within 48 hours and the central team responsible for case classification. Fourth, PATH developed buy-in among local stakeholders, conducting sensitization and planning workshops for district magistrates, chief medical officers, pediatric physician associations, and media. When unfounded rumors concerning the safety of the vaccine began to circulate among Indian media, MHOFW was able to respond in timely manner and rebut those rumors with data and the support of local physicians. PATH estimates it spent approximately \$30 per each of the 6000 adverse events reports generated through pharmacovigilance campaign, not including its modest staff costs.

In sum, pharmacovigilance for the JE vaccine in India succeeded because it was locally developed and supported, training occurred in the context of addressing a specific health need rather than in the abstract, and local officials valued the program because it worked and was affordable. Six years later, 83 million children in India have been vaccinated for JE. Many credit the JE campaign for catalyzing the relatively robust pharmacovigilance system that now exists in India.

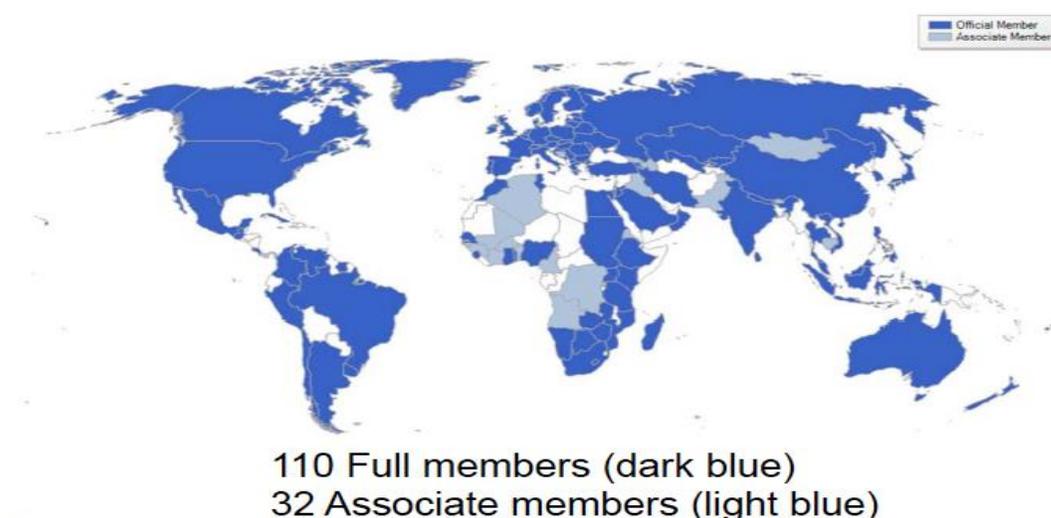
Leverage Existing Infrastructure

As the risk-based analysis in the previous section of this report demonstrated, many of the countries that will host the greatest number of higher-risk drug and vaccine introductions have some minimal pharmacovigilance structures. In many cases, this infrastructure may be harnessed to respond to countries' present needs and support sustainable pharmacovigilance programs such as stimulated passive surveillance and active surveillance, including cohort event monitoring, case controlled studies, and observational studies. That infrastructure may include:

The International Drug Monitoring Program. Even if the international pharmacovigilance capability building initiatives do not rely primarily on passive safety surveillance, this long-standing program

provides infrastructure and capacity that can be leveraged. This includes: a designated point of government contact for pharmacovigilance matters, basic familiarity with pharmacovigilance concepts, and internationally consistent tools for case reporting, including the WHO Drug Dictionary, WHOART, and VigiFlow. More than 100 countries, including 26 percent of low- and lower-middle income countries, are registered members in the Program. Similarly, the WHO Global Vaccine Safety Initiative, the Brighton Collaboration, CIOMS/WHO Working Group on Vaccine Pharmacovigilance, and other initiatives provide training programs, standardized adverse event definitions, and monitoring guidelines that should also be leveraged in support medical product introduction and capacity building.

The WHO PV Programme



Epidemiological sentinel sites and clinical trial networks. Clinical trial and epidemiological sentinel sites exist in most LMIC settings and have infrastructure – trained staff, laboratory infrastructure, and, in some instances, health and demographic data on local populations – that could be leveraged to detect, assess, and communicate serious concerns regarding novel and newly introduced drugs and vaccines. In some instances, these sites are already organized into networks in countries of interest. The International Network for the Demographic Evaluation of Populations and Their Health (INDEPTH) network, for example, is a loose collection of demographic research institutions that exist in many of the South Asian and East and West African countries that the risk-based analysis has revealed are expected to host disproportionate number of launches of higher risk drugs and vaccines. A small pilot project is currently being conducted to assess the capability of the INDEPTH network to support pharmacovigilance activities. The National Institutes of Health sponsored International Epidemiologic Database to Evaluate HIV/AIDS (IeDEA) cohort network offers the potential to provide pharmacovigilance relevant information.⁷⁸

⁷⁸ Miller V, Nwokike J, Stergachis A. Pharmacovigilance and global HIV/AIDS. *Curr Opin HIV AIDS*. 2012 Jul;7(4):299-304.

Currently 37 sites in 19 countries

- 21 sites in Africa
- 9 sites in Asia
- 1 site in Oceania
- 1 site in Latin America



Over 2,000,000 people under surveillance

***Countries with Demographic Surveillance System (DSS)
Field Sites participating in the INDEPTH Network***

Pregnancy registries. Some developing countries are pilot testing registries to monitor outcomes of pregnancies following exposure to treatment with pharmaceuticals such as HIV/AIDS and malaria medications. Some of these registries exist in priority countries, can serve as sentinel sites, and presently collect data on pregnancy exposures and outcomes in a systematic manner.⁷⁹ For example, a major unresolved safety concern for malaria case management is the safety of the use of ACTs in the first trimester of pregnancy – a topic under investigation at sentinel sites in Kenya, Mozambique, and Burkina Faso.⁸⁰

Local hospitals, clinics, and laboratory facilities. Local hospitals and clinics exist in most LMICs. These institutions provide platforms for conducting case-series and case-control programs to assess the association among pre-defined priority conditions, adverse events, and the administration of a drug or vaccine of interest.⁸¹ Few developing countries have capable national laboratories, but some exist, for example in Kenya and South Africa, and could be leveraged for diagnostic activities. Records linkage in support of pharmacovigilance is possible where drug, laboratory and medical records exist in LMICs.⁸² Engaging and funding the existing capable national laboratories and hospitals builds diagnostic capacity that supports priority products and longer-term regional drug and safety needs.

⁷⁹ WORLD HEALTH ORGANIZATION, THE WORLD MEDICINES SITUATION: PHARMACOVIGILANCE AND SAFETY OF MEDICINES (2011).

⁸⁰ Dellicour S, ter Kuile F, Stergachis A. Pregnancy Exposure Registries for Assessing Antimalarial Drug Safety in Pregnancy in Malaria Endemic Countries. PLoS Medicine. Vol. 5, No. 9, e187 doi:10.1371/journal.pmed.0050187.

⁸¹ See, e.g., Manish M. Patel et al., Intussusception Risk and Health Benefits of Rotavirus Vaccination in Mexico and Brazil, 364 NEJM 2283 (2011).

⁸² Corbell C, Katjita I, Sagwa E, Mabilirizi D, Nwokike J, Mengistu A, Lates J, Fuller S, Stergachis A. Records linkage of electronic data bases for the assessment of adverse effects of antiretroviral therapy in Namibia. Pharmacoepi Drug Safety. 2011 Oct 19. doi: 10.1002/pds.2252.

Academic institutions. Capable academic personnel and programs exist on pharmacovigilance in some LMICs.⁸³ Enlisting local capable academic personnel and programs in supporting the post-market surveillance of high-priority products can enhance their ability to advise on the design of capacity building programs, train government personnel and local health professionals, assess serious adverse events, and conduct pharmacoepidemiological studies.

Promoting Buy-In

Improving local government and stakeholders' commitment to pharmacovigilance will require a combination of strategies. A necessary first step to convincing LMIC governments to prioritize pharmacovigilance is for the global health community to better demonstrate that it is one. Donors, development institutions, and international technical agencies will need to commit more political capital and resources to elevate pharmacovigilance beyond regulatory agencies to the level of health and industry ministers. The political commitment of such ministers should be obtained before donors invest in local pharmacovigilance capacity. The Global Fund has invited funding proposals on pharmacovigilance and GAVI has required recipient countries to implement an adverse event surveillance system, but these and other treatment and immunization programs will need to be more persistent in insisting that recipients have functioning pharmacovigilance programs. Previous analysis of Global Fund – Malaria proposals and PMI Malaria Operational Plans showed that there were relatively few requests for funding for pharmacovigilance activities, demonstrating a lack of emphasis placed on pharmacovigilance systems in recipient countries and stressing the need for more active direction to strengthen active surveillance and passive adverse event reporting systems to augment the issuance of guidance documents.⁸⁴

Second, and as discussed above, local governments and stakeholders must be engaged as full partners in the conception and implementation of pharmacovigilance programs and capacity building efforts. These programs should be feasible given local conditions and responsive to local needs. Pharmacovigilance programs that are useful, effective, and have been developed with the input of stakeholders and LMIC governments are more likely to be valued and maintained.

Third, donors and development agencies should consider creating incentives to convince LMIC governments to prioritize pharmacovigilance despite competing health priorities and resource scarcities. These incentives could promote outcome-driven, bottom-up approaches to pharmacovigilance in developing countries to complement the top-down, policy-driven approach of many international pharmacovigilance initiatives.

One possible approach would be establishing a prize fund for pharmacovigilance similar to the Race to the Top fund currently operated by the U.S. Department of Education. U.S. state governments compete for supplemental prize funding based on which government develops the most promising

⁸³ For a list of academic institutions and other in-country organizations with pharmacovigilance activities and capabilities in sub-Saharan Africa see SAFETY OF MEDICINES IN SUB-SAHARAN AFRICA, *supra* note 32.

⁸⁴ Stergachis A, Bartlein R, Doodoo A, Nwokike J, Kachur SP. A situational analysis of pharmacovigilance plans in the Global Fund Malaria and U.S Presidents' Malaria Initiative proposals. *Malaria J.* 2010; 9:148.

proposal for comprehensive education reform programs.⁸⁵ Another possibility would be a matching grant program in which donors contribute funding that is equal to the amount that a government invests in upgrading its pharmacovigilance programs. Yet another possible approach would be “challenge grants,” which link the establishment of competent pharmacovigilance systems to broader development aid or multilateral development bank lending as a way to elevate post-market drug or vaccine safety on the agenda of ministries of finance. More research is needed to assess the appropriateness and effectiveness of such incentives to promote medical product regulation. The issue of funding for such approaches is discussed in the next chapter.

Integrate investments in drug and vaccine pharmacovigilance

Post-market drug- and vaccine-safety surveillance is conducted separately in many countries through parallel and often poorly coordinated systems. While vaccine regulation typically falls under the oversight of a country’s drug regulatory authority, the programmatic aspects of immunization programs - including monitoring, reporting, and analysis of adverse events following immunization (AEFIs) - are usually separate from a country’s national pharmacovigilance center. These activities are typically carried out by a country’s specific public health program, such as its expanded program on immunization (EPI), often with insufficient linkages with national pharmacovigilance centers that primarily focus on drugs. Coordination and communication between drug and vaccine authorities responsible for safety can be limited.⁸⁶ In many countries, AEFIs detected and reported by EPI are not commonly shared with national pharmacovigilance centers.⁸⁷

There are differences between vaccines and drugs that deserve consideration when planning and conducting pharmacovigilance activities. Their uses are often different. Vaccines are generally administered to large numbers of healthy, young persons (particularly infants and children) and the public is often less willing to accept risk associated with that vaccine, particularly in settings where the disease at issue is decreasing in prevalence. Some drugs are used for acute conditions, such as enteric and diarrheal diseases, while others are taken on an iterative and extended basis for chronic conditions, such as HIV/AIDS. Drugs and vaccines pose different transport and delivery risks. Vaccines often require consistent refrigeration to retain potency and are subject to injection errors. Quality of care issues with drugs can arise from errors not only in administration, but also in prescribing, dispensing, and patient adherence to regimens. Evaluating safety data for vaccines and drugs requires different expertise to conduct causality assessment.

While the differences between drugs and vaccines should be taken into account in the design of pharmacovigilance activities, benefit-risk assessment, and risk communication, these differences do not necessitate entirely separate systems. Both require ongoing evaluation of benefit-risk throughout the product’s life cycle. Many of the tools, techniques and resources needed for adverse event case

⁸⁵ <http://www2.ed.gov/racetothetop/index.html>

⁸⁶ Letourneau M, Wells G, Walop W, et al. Improving Global Monitoring of Vaccine Safety: A Survey of National Centres Participating in the WHO Programme for International Drug Monitoring. *Drug Safety*. 2008; 31: 389-398.

⁸⁷ Labadie J. Sharing AEFI reports: pharmacovigilance centres and national immunization programmes. *Uppsala Reports*. 2012; 56:7.

collection and handling are the same for both drug and vaccine pharmacovigilance. There is little inherently different in the post-market safety surveillance of these products that necessitates entirely separate passive surveillance systems, reporting forms, databases and procedures for data analysis and review, and other infrastructure and processes for causality assessment. There is also no reason to believe that investments in risk communication and management, staff training and development, and health care provider and public education could not be pursued in a manner that would yield compound benefits for drug and vaccine safety surveillance programs.

Although many countries conduct post-market drug- and vaccine-safety surveillance separately, there are precedents for integrated approaches. Health Canada has successfully combined its system for collecting adverse events reports for drugs and vaccines into a linked database. FDA has a mini-sentinel initiative that draws on existing automated healthcare data from multiple sources to actively monitor the safety of medical products generally, continuously and in real-time.⁸⁸

In countries where little post-market safety surveillance capacity exists, there seems little reason to spend scarce resources to establish separate drug and vaccine post-market safety surveillance systems. While the authors are unaware of any analysis of the cost- and time-savings for conducting combined drug and vaccine safety surveillance, it is logical to assume that training personnel and establishing and maintaining databases in an integrated fashion would be noticeably more efficient.

Pharmacovigilance conducted in support of medical product introduction in LMICs should pursue capacity building efforts for drugs and vaccines in a manner that promotes integration. One effective way to do so is to train inclusively wherever possible. In the post-market safety surveillance conducted in support of a novel vaccine, local drug safety officials should be included in the elements of training and development and implementation of plans that have equal relevance for them. The reverse is also true.

Cooperative Approaches

Cooperative approaches offer several potential benefits for sustainably improving pharmacovigilance capacity in LMICs. Cooperation among national regulatory authorities and/or public health programs pools their scarce resources and expertise. Sharing data and collaborative decision-making are powerful ways to promote regulatory convergence and the use of common documentation and terminology. Finally, cooperative initiatives provide a more sustainable and attractive platform for donor investment and technical assistance, spreading the resulting benefits across multiple beneficiaries and reducing the need for duplication.

Such cooperation, however, is not without significant challenges. Governments value their sovereignty in regulatory and public safety matters and are understandably protective of the

⁸⁸ FDA's Sentinel Initiative – Background, available at <http://www.fda.gov/Safety/FDAsSentinelInitiative/ucm149340.htm> (last visited Aug. 19, 2012). Nguyen M, Robert Ball R, Karen Midthun K, et al. The Food and Drug Administration's Post-Licensure Rapid Immunization Safety Monitoring program: strengthening the federal vaccine safety enterprise. *Pharmacoepidemiology and Drug Safety*. 2012;21(S1):291–297.

independence and local accountability of their officials. Effective cooperation takes time, requires supporting infrastructure and administration, and involves the sustained investments of political will and staff-level commitment.

Accordingly, international or regional cooperation on pharmacovigilance should not be considered an end in itself. International regulatory cooperation has proven most effective when it is necessary for the participants in order to achieve their respective regulatory objectives, initially limited, linked to existing structures, and respectful of the participants' sovereignty and need for local accountability.⁸⁹ Applying these criteria to the pharmacovigilance context suggests potential opportunities may exist in the following areas.

Joint development of post-market safety surveillance plans. Many LMIC regulators and public health authorities do not yet have the expertise and human resources necessary to develop pharmacovigilance plans for novel and newly introduced vaccines and drugs. Engaging peer regulators in the design and implementation of pharmacovigilance programs promotes regional convergence and capacity on post-market safety surveillance. The WHO African Vaccine Regulatory Forum (AVAREF) used similarly inclusive joint reviews of clinical trial application to build capacity of less experienced national regulatory authorities.

Consistent approaches to data. Treatment and immunization programs could work closer with national regulatory authorities, technical agencies, PDPs, and industry to adopt standardized criteria on the collection, storage, codification, and reporting of safety concerns. These criteria should be simple, initially limited in scope, and feasible for use in most low- and middle-income countries. To the extent possible, these criteria should be based on international norms and standards.⁹⁰ Treatment and immunization programs should share surveillance and analytic tools employed in the introduction of a new drug and vaccine with other such initiatives, in order to promote consistent case definitions, more standard management and assessment procedures, and use of common reporting and investigation forms. Using consistent approaches to estimate population background rates particularly on common serious adverse events would improve the utility of that data for causality assessments in other drug and vaccine safety concerns. It would also promote more efficient use of scarce resources, reduce the need for duplicative training, and facilitate coordinated action among participating governments, institutions, and global health programs.

Collaborative databases and review. Sharing and collaboratively analyzing pharmacovigilance data has numerous benefits. The populations that can be monitored through one country's sentinel sites are often too small to identify significant adverse events potentially associated with the administration of

⁸⁹ See SAFER, FASTER, CHEAPER: IMPROVING CLINICAL TRIALS AND REGULATORY PATHWAYS TO FIGHT NEGLECTED DISEASES: REPORT OF CENTER FOR GLOBAL DEVELOPMENT WORKING GROUP ON CLINICAL TRIALS AND REGULATORY PATHWAYS (2011) for analysis of the various precedents for international regulatory cooperation on medical trial registration and clinical trial oversight.

⁹⁰ INSTITUTE OF MEDICINE, ENSURING SAFE FOODS AND MEDICAL PRODUCTS THROUGH STRONGER REGULATORY SYSTEMS ABROAD (2012) (citing WHO-ART, Anatomical Therapeutic Chemical (ATC) classification), and identification of medicinal products (IDMP) standards as the fundamental tools for enhancing compatibility for the exchange of drug safety information).

the drug or vaccine. Alternatively, the adverse event may be serious, but relatively rare and detection demands a population size that exceeds the number of individuals who received that product in that country. Finally, many LMICs do not yet have the expertise and resources to conduct these activities on their own.

Precedents for peer regulators working collaboratively on post-market safety data collection and analysis exist. The Pan American Health Organization (PAHO) recently launched a regional platform where capable regulatory authorities share adverse event reports and safety data and may work together on its analysis. The Global Vaccine Safety Data Network performed a collaborative data-based analysis of the risk of Guillain Barre Syndrome for pandemic flu vaccines in 18 countries.⁹¹ The Asia Pacific Economic Community (APEC) is also working to develop a more coordinated system to ensure that safety information on drugs is adequately collected, impartially evaluated in the context of risks and benefits, and made accessible to all participating countries. The Malaria in Pregnancy Consortium and the ACT Consortium established a coordinated centralized pharmacovigilance database and supportive infrastructure for a multitude of research studies being conducted in numerous sites in SSA and elsewhere in the tropics.⁹²

Clinical diagnosis and causality assessment. Clinical diagnosis and causality assessment in pharmacovigilance requires biomedical expertise and clinical and pharmacological experience that is in limited supply in some LMICs. Joint approaches to these activities would offer the potential to pool participating regulatory authorities' capacity, promote convergent approaches, and provide a more efficient platform for technical assistance.

Supporting centers for excellence. In some instances, such as where pharmacovigilance challenges are specific to a particular country, a supporting center for excellence would be a useful complement to joint approaches. In this model, a regional institution would maintain a few in-house technical experts that are available to consult with participating governments' regulatory and public health authorities on designing and implementing programs to detect, assess, and respond to a priority drug or vaccine safety concerns. Such regional structures will require seed funding from donors, but should be self-supporting over the long term. Financing options are discussed in the next section of this report.

⁹¹ Steven Black et al., Post-licensure evaluation of vaccine safety: Current status and future directions, Biologicals 1-2 (2011).

⁹² www.mip-consortium.org and www.actconsortium.org.

How to Invest

The novel and newly introduced drugs and vaccines that will be introduced in developing countries over the next decade are by no means the only pharmacovigilance challenges that these countries face.⁹³ Many LMICs are also growth markets for pharmaceutical sales, including products manufactured in countries with still nascent regulatory systems. Substandard, falsified, and counterfeit medicines are a significant problem in many LMICs. The proliferation of such products harms patients, diminishes the therapeutic effectiveness of critical treatment and prevention, and is contributing to the rise of resistance, for malaria drugs in particular.⁹⁴ These post-market safety needs are chronic and not predictable with the same precision, but also important to address.⁹⁵

Given limited resources and pressing needs, initiatives to strengthen post-market safety surveillance in LMICs should be prioritized, but must be scalable to the broader health needs of these countries and populations. Scalability should be pursued in three ways.

First, pharmacovigilance conducted in support of the introduction of a novel or new-to-market drug or vaccine should be designed not only address the particular post-market safety needs of that product, but also to build the robust surveillance, reporting, signal evaluation and benefit-risk management, and laboratory systems needed for monitoring the safety, effectiveness, and quality of all medications in that setting. The strategies outlined in the previous section – leveraging and investing in existing infrastructure, promoting consistent approaches to data, and training inclusively – are important ways to start building broadly capable pharmacovigilance systems.

Second, pharmacovigilance conducted in support of the introduction of a novel or new-to-market drug or vaccine should support the broader post-market safety surveillance needs in other countries. Drug and vaccine distribution is expanding among LMICs generally, not only in the countries that will be identified as priorities in a risk-based analysis of the global health product pipeline. Increasing information and data exchange and promoting regional cooperative approaches would improve the safety and quality of medicines among all participating regulatory authorities.

Third, the scalability of post-market safety surveillance systems in LMICs depends on predictable and sustainable funding for training, infrastructure, and staff. Funding will not be forthcoming or sustained, however, without improving and demonstrating the effectiveness of international initiatives to strengthen post-market safety surveillance in developing countries. Accordingly, post-market safety surveillance initiatives must be subject to monitoring, evaluated, and adjusted to respond to deficiencies in performance and local demands.

⁹³ Bakare et al., *supra* note 39.

⁹⁴ Gaurvika et al., *supra* note 18.

⁹⁵ It is worth noting that initiatives exist to better track the distribution of substandard, falsified, and counterfeit medicines, particularly malaria. See <http://www.wwarn.org/>.

Predictable and sustainable financing

Post-market safety surveillance has been an area of underinvestment in many LMICs. The fees that most developing country governments currently charge for licensing drugs and vaccines are modest and insufficient to fund the range of regulatory activities needed in these settings. Most developing country governments do not charge fees specifically for pharmacovigilance.

There may be a window of opportunity for increasing support for post-market safety surveillance in LMICs. National regulatory authorities, marketing authorization holders, and global health donors have a common interest in ensuring that novel medicines that will be introduced over the next decade do not unnecessarily harm patients and that treatment and immunizations programs are conducted as effectively as possible. These drugs and vaccines have tremendous potential to save lives and reduce suffering among the world's poor and vulnerable. Tremendous resources have been devoted to their discovery, development, and delivery.

However, the competing demands on donor, industry, and developing country government resources are many and the precedent for aid for regulatory capacity building is limited. The prospects of obtaining the necessary support and technical assistance will be much enhanced if (1) the funding required is modest and that burden is shared among stakeholders; (2) the donor funding needed is catalytic and limited in duration; (3) local country ownership is established from the outset; and (4) the funding arrangement is self-sustaining, at least over the long-term.

The amount of funding needed to strengthen post-market safety surveillance in LMICs will depend on the strategies employed and the countries involved. The strategies outlined above on prioritization and sustainability would help reduce that amount. The identity of contributors and the appropriate vehicles for receiving and distributing funds are matters for stakeholder consultation; the financing model below is provided to help initiate that discussion.

Catalytic/seed funding. Invariably, some seed funding will be needed to develop the basic human resources and the infrastructure required for functional, scalable pharmacovigilance programs. That seed funding would likely need to come primarily from philanthropic sources, development banks, industry, and governments concerned with global health and economic development.

To be effective, seed funding commitments must be predictable and multi-year. This funding support could be provided in a manner similar to the African Medicines Regulatory Harmonization (AMRH) initiative.⁹⁶ Donors could contribute to a trust fund maintained by the World Bank or another host institution. The expenditure of those funds could be made through a regional implementing partner, such as a regional economic community or health institution, with technical support from WHO and others, and an advisory committee of academics and other technical experts, developed country regulators, patient advocates, and donors. Pooling funding from multiple donors in a trust fund maintained by a third party and using another intermediary to direct and

⁹⁶ www.amrh.org.

distribute that funding would greatly reduce the real or perceived risk of conflicts of interest from industry contributions.

Country Ownership. Co-financing should be sought from participating governments from the outset. Increasingly, global health initiatives require recipient government contributions as a condition of participation. Countries participating in UNICEF's procurement mechanism are required to pay between 3 and 6 percent of their vaccines' purchase value to cover administrative costs.⁹⁷ The PAHO Revolving Fund charges member states a recapitalization fee of 3.5 percent in addition to the overall vaccine price. GAVI requires even the poorest recipient countries to co-finance the procurement of vaccines. These contributions ensure the establishment of national budget lines and sustainable recipient government support for programs. Early investment helps prepare participating governments for the inevitable phasing out of donor support.

Here too, the amount of co-financing contributions for strengthening post-market safety surveillance in LMICs should be based on the ability of a government to pay, as determined by World Bank data on the country's per capita Gross National Income. The poorest countries should contribute the minimum amount. Countries that exceed a certain income level should be encouraged to self-finance their continued participation in training programs and cooperative approaches to post-market safety surveillance.

Some portion of donor funds could be distributed to participating governments through matching grants. GAVI operates a similar matching grant program in its advance market commitment for pneumococcal vaccines. LMICs that fund sustainable and scalable post-market safety surveillance programs would be eligible to apply for matching grants. The amount of those matching grants could be tied to the income status of the country.

Fees. Fees are widely used to fund medical product regulation.⁹⁸ EMA has recently proposed dedicated fees to fund its pharmacovigilance activities.⁹⁹ Fees offer two potential benefits for supporting LMIC pharmacovigilance systems. First, it provides a sustainable source of funding for a chronically and significantly underfunded area. Second, it increases the accountability of governments to fee-payers for the performance and improvement of their pharmacovigilance systems. For both reasons, it is important that industry and global health programs alike are subject to fees to ensure their engagement and the sustainability of the post-market safety surveillance system.

⁹⁷ The World Bank and GAVI Alliance, *The Vaccine Market – Pooled Procurement*, in *Immunization Financing Toolkit*. December 2010. http://www.who.int/immunization_financing/tools/Brief_12_Pooled_Procurement.pdf, (4 June 2011), page 2.

⁹⁸ See, for example, the U.S. Prescription Drug User Fee Act (PDUFA) enacted in 1992 and renewed in 1997 (PDUFA II), 2002 (PDUFA III), 2007 (PDUFA IV), and 2012 (PDUFA V). Under sections 735 and 736 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. §§ 379g and 379h), FDA has the authority to assess and collect user fees for certain drug and biologics license applications submitted to the agency for review. FDA sets these fees on a yearly basis.

⁹⁹ European Commission, *Introduction of Fees to be Charged by EMA for Pharmacovigilance*, Concept Paper Submitted for Public Consultation (2012).

Fees could be assessed in three ways, which are not mutually exclusive. A national regulatory authority could charge an additional lump sum fee for pharmacovigilance as part of drug and vaccine registration. Alternatively, the fee could be tied to the volume of drugs and vaccines sold or distributed.¹⁰⁰ Finally, the fee could be tied to the risk of the product. The proposed EMA fee is risk-based, charged as part of evaluation of safety update reports. Whichever approach is used, fees in LMICs should not be designed in a manner that discourages safety reporting or distribution of lifesaving treatment or prevention tools for patients without other options.

Monitoring and evaluation

Donor and industry funding for strengthening post-market safety surveillance will not be forthcoming or sustained without improving and demonstrating the effectiveness of the results. Accordingly, initiatives to improve pharmacovigilance capacity should be monitored, evaluated, and adjusted on an ongoing basis according to emerging evidence regarding their performance.

The design of the monitoring and evaluation program will depend on the specifics of the initiative. Broadly speaking, monitoring would involve collecting data on validated, pre-determined indicators and analyzing it to verify whether pharmacovigilance programs were implemented according to plan, whether financial resources and inputs were applied as intended, whether the expected outputs and impact were realized, and in the time expected.¹⁰¹ More work is needed to define indicators of impact of PV systems, but possible process indicators might include number of ADR reports shared with regional and WHO databases, the adoption of international, harmonized standards for data collection and reporting, and training conducted. Data would be collected during implementation and execution of the project. The assessment of that data would assist in identifying inefficiencies and making adjustments in real time.

¹⁰⁰ The Vaccine Injury Compensation Trust Fund, which was first implemented in the United States in 1988 to cover claims following severe cases of AEFI, is financed by a 0.75 excise tax on each individual vaccine dose purchased. http://www.hrsa.gov/vaccinecompensation/VIC_Trust_Fund.htm.

¹⁰¹ See generally Center for Global Development, Report of the Evaluation Gap Working Group, When Will We Ever Learn? Improving Lives through Impact Evaluation (Savedoff, Levine, Birdsall eds. 2006).

Toward Implementation

The drugs and vaccines now beginning to reach LMICs have the potential to revolutionize the health care in these settings, reduce avoidable deaths and infirmity, and afford millions the opportunity to lead productive lives. Achieving that potential will depend, however, on adequate monitoring of the safety of these medicines post-approval and ensuring favorable benefit-risk profiles throughout the medical product lifecycles.

The way forward on strengthening post-market safety surveillance in LMICs is not to define the particular combination of stimulated passive safety surveillance and active pharmacovigilance techniques that should be applied in every country or to every novel or new-to-market product introduction. Not all the strategies outlined in this report, such as integrating drug and vaccine safety surveillance or leveraging existing demographic safety surveillance sites, will be appropriate or possible in all settings and circumstances.

The way forward is for the relevant stakeholders to recognize that adequate post-market safety surveillance in LMICs is critical to global health and that global health product introduction represents both a critical need and opportunity for strengthening that surveillance. Addressing that need and capitalizing on that opportunity will require better data to prioritize investments and increased coordination, funding, and training and technical assistance to build sustainable, scalable post-market safety systems.

Better Data

Information on the introduction plans for the candidate drugs and vaccine in the global health product pipeline is scarce and not generally shared with other global health product developers, international technical agencies, and the host countries themselves. Building post-market safety surveillance takes time and advance planning. Marketing authorization holders should not be expected to build these systems alone nor develop protocols for in-country post-market safety studies without engaging in a consultative process with relevant stakeholders. More and better data would allow donors, international technical agencies, and governments to plan, prioritize, and take advantage of the potential synergies that may exist as a result of multiple product introductions. For instance, the current, admittedly incomplete data analyzed in this report suggests that clusters of countries in East Africa, West Africa, and South Asia will host the greatest number of higher-risk drug and vaccine introductions and many of these countries have limited capacity to do so. This risk-based pipeline assessment should be updated regularly and incorporated into planning.

More Coordination

The analysis in this report suggests that many of the same countries will host multiple introductions of novel and new-to-market drugs and vaccines over the next decade. Improving coordination in the post-market safety surveillance conducted in support of these product introductions would reduce the need for duplicative investments and exploit potential synergies for building pharmacovigilance in those countries and their regions. Increased coordination is possible as many of these product

introductions will occur with the support of the same few donors and treatment and immunization programs. Donors and programs should work with a small group of national regulatory authorities, technical agencies, PDPs, and industry representatives involved in the forthcoming global health product introductions to adopt common reporting and investigation forms and standardized criteria on the collection, storage, codification, and reporting of safety concerns. These forms and criteria should be simple, limited in scope, and feasible for use in most LMICs. To the extent possible, these criteria should be based on international norms and standards.

A multi-donor trust fund for pilot programs

Post-market safety surveillance is new to many LMICs. The strategies in this report for building sustainable and scalable post-market safety surveillance systems are promising, but must be tested. These strategies should be piloted in support of novel and new-to-market product introduction, monitored, evaluated, and adjusted in response to performance. A multi-donor trust fund should be established, or a portion of an existing trust fund earmarked, for funding such pilots.

Contributors to the multi-donor fund should include bilateral development agencies, global health programs and intermediaries (e.g., GAVI, Global Fund), multinational pharmaceutical industry, multilateral development banks, and philanthropic foundations. Ensuring inclusive participation will improve the resources of the fund and encourage widespread ownership in the capacity building programs funded. Broad participation and a pooled funding arrangement should help avoid the possible conflicts of interest that might otherwise arise. Funds from the multi-donor trust fund should be distributed in the form of matching grants to product developers and LMIC governments. This arrangement will reduce recipient dependence on the trust fund and ensure stakeholder ownership in post-market safety surveillance.

Regional technical facilities

Industry, developed country regulators, academia, and technical agencies have tremendous expertise that could help product sponsors and LMIC regulators implement the strategies outlined in this report, including on training, data sharing, and fee arrangements. Technical advisory facilities should be established to provide this expertise in priority regions. Intermediary entities, such regional public health and economic institutions, should host the facility and help ensure active participation. These facilities could also function as centers of excellence and facilitate sharing of safety reports and exchange of benefit-risk management strategies. The multi-donor trust fund should provide the resources for hosting and managing these technical advisory facilities.

Realizing these complementary strategies will require collaboration and investment from all key stakeholders. These contributions must include:

From global health product sponsors: early identification of the likely countries where their candidate drugs and vaccines will be introduced, estimates of the likely patient exposure, and assessment of the launch countries' pharmacovigilance capacity; a willingness to update and share that data with donors and international technical agencies as clinical development progresses; and investment of

upfront resources to implement the strategies in this report for supporting sustainable post-market surveillance.

From global health programs and intermediaries: more effort to require, prioritize, and support adequate post-market safety surveillance among participating LMICs, including providing funding and technical support for product introduction and longer-term capacity building.

From LMIC regulatory authorities and public health programs: a political commitment to adequate post-market safety surveillance, including, where possible, a contribution of funding and personnel; a willingness to work with product sponsors, as appropriate, to build sustainability and scalability into post-market safety surveillance conducted in support of novel and new-to-market drug and vaccine introduction; a willingness to engage external expertise, when needed; a willingness to institute adequate fees, where possible, to support post-market safety surveillance; and a commitment to data exchange and the cooperative efforts with peer regulators that can pool capacity and promote convergent approaches.

From donors: acceptance of adequate post-market safety surveillance as a priority for global health and product introduction; requiring product development grantees to prioritize post-market safety in their planning and to share those plans with donors and international technical agencies; seed funding to launch post-market safety surveillance programs and cooperation among peer regulators; and support for training, surveillance sites, and other sustainable infrastructure investments that can improve the adequacy of post-market safety oversight.

From the multinational pharmaceutical industry: a willingness to provide technical assistance to LMIC regulatory authorities to support adequate post-market safety surveillance; a willingness to contribute to a multi-donor trust fund to pilot programs.

From developed country regulators and international technical agencies: sustained investment in technical assistance and diplomatic support for national and regional approaches to improve post-market safety surveillance in LMICs, including increasing technical assistance for LMICs addressing the post-market safety demands of the global health product pipeline.

The prospects for generating these contributions from stakeholders are improving. Opportunities for partnerships exist. Global health product development is motivating new donor resources and technical assistance for regulatory capacity building in developing countries. There are a growing number of initiatives to strengthen post-market safety surveillance capacity generally in LMICs. Numerous regional economic and health institutions in Asia and Latin America are already cooperating on regional approaches to pharmacovigilance. Regional economic communities in Africa are pursuing harmonization of drug registration as part of the AMRH initiative. The World Bank has created a trust fund, with \$12.5 million in seed funding from the Bill & Melinda Gates Foundation, which supports some of these efforts. Substantial and increasing private industry investment is devoted to selling drugs and vaccines in these markets. The time for action is now.

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Annex

Examples of assessment of potential post-market risks associated with drugs and vaccines in the current global health product pipeline

A. High Risk Level for Pharmacovigilance

116E Neonatal Strain (P[11].G9 Rotavirus Vaccine

A rotavirus vaccines derived from the Indian human neonatal strain, strain 116E, P[11]G9 human–bovine reassortant strain is currently under Phase III study. In a trial of approximately 200 persons, there were no significant differences between the vaccine group and the placebo group in the proportion of infants who had expected adverse events that were adjudged to be probably, possibly, or remotely related to the vaccine.¹⁰² Unexpected and expected adverse events were monitored during the 2-week follow-up period. Fifteen severe adverse events were reported with the vaccine; none of these events were assessed to be vaccine-related nor did any cases of intussusception occur. However, severe but uncommon adverse effects, such as intussusception, would only become evident during larger trials or during post-marketing surveillance. The WHO recommends that post-marketing surveillance for rare adverse events, including intussusception, for rotavirus vaccines.¹⁰³ This is because a previous rotavirus vaccine (Rotashield) was associated with a ~30-fold increase in risk of intussusception during the week following receipt of the first vaccine dose. Subsequent rotavirus vaccines (Rotarix and RotaTeq) demonstrate a good safety profile, but may be associated with an increased (up to 6-fold) risk of intussusception after the first dose of vaccine in some populations - a level of risk observed are substantially less than those observed with the previous vaccine, Rotashield. The WHO Global Advisory Committee on Vaccine Safety indicates that active surveillance of intussusception in African and Asian countries that plan to introduce rotavirus vaccines should be seriously considered, because the data accrued would eventually provide additional benefit–risk information related to these important vaccines.¹⁰⁴

B. Medium Risk Level for Pharmacovigilance

Meningococcal A conjugate vaccine, (MenAfriVac)

MenAfriVac was approved in 2010 and approval in 2014 anticipated for < 1 year olds. Reports of bronchospasm and urticaria may suggest hypersensitivity reactions to vaccination. Following a review of new data for MenAfriVac, WHO's Global Advisory Committee on Vaccine Safety concluded that the experience from the first 3 countries to introduce this vaccine did not indicate any reasons for concern about the vaccine's safety.¹⁰⁵ The data reviewed by the Advisory Committee — at its meeting of June 15-16, 2011 — were collected in Burkina Faso, Mali and Niger during the September and December 2010 vaccination campaigns and from the surveillance systems. Active surveillance for 12 pre-identified syndromes was conducted for 52 days (10 days during the vaccination campaign and 42 days after) in 16 health-care facilities in which approximately 100,000

¹⁰² Bhandari N, Sharma P, Taneja S, et al. A Dose-Escalation Safety and Immunogenicity Study of Live Attenuated Oral Rotavirus Vaccine 116E in Infants: A Randomized, Double-Blind, Placebo-Controlled Trial. *JID*. 2009; 200:421–9.

¹⁰³ World Health Organization. Report of the Global Advisory Committee on Vaccine Safety. *Wkly Epidemiol Rec* 2006;81:13-20

¹⁰⁴ Global Advisory Committee on Vaccine Safety, report of meeting held 7-8 December 2011. http://www.who.int/vaccine_safety/reports/Dec_2011/en/index.html (accessed May 23, 2012).

¹⁰⁵ WHO. Weekly epidemiological record. 22 July 2011, No. 30, 2011, 86, 317–324. <http://www.who.int/wer/2011/wer8630.pdf>

people had been vaccinated. A total of 71 episodes of these syndromes were investigated, of which the most common were convulsion (32 cases), urticaria (18) and bronchospasm (14). The national expert committee of Burkina Faso classified these cases as coincidental. For the 3 most frequent syndromes, the distribution of the intervals between vaccination and the occurrence of symptoms did not reveal any temporal clustering. The Advisory Committee also highlighted the need for continuous surveillance as the vaccine is rolled out to ensure that further data on the safety profile of the vaccine can be obtained.

C. Low Risk Level for Pharmacovigilance

Artemether-Lumefantrine - (Coartem Dispersible)

The dispersible formulation of Coartem specifically designed for children was approved by Swissmedic in December 2008, following a large phase III trial. Considerable post-marketing experience and surveillance is available on Coartem as the drug has been in use since 2001 with hundreds of millions of doses distributed. The primary safety concerns with Coartem are hypersensitivity and skin reactions (allergies). Also, Coartem is contraindicated in the first trimester of pregnancy in situations where other suitable and effective anti-malarials are available. Investigators have reported a good safety profile with Coartem Dispersible.¹⁰⁶ The most common drug-related adverse event was vomiting (n=33 [7%] and n=42 [9%] for the dispersible (n=447) or comparator crushed tablets (n=452), respectively. No signs of ototoxicity or relevant cardiotoxicity were seen.

¹⁰⁶ Abdulla S, Sagara I, Borrmann S, et al, Efficacy and safety of artemether-lumefantrine dispersible tablet in African infants and children with uncomplicated malaria: a randomised, investigator-blinded, multi-centre comparison with the crushed commercial tablet; *The Lancet*. 2008 Nov 22;372(9652):1819-27.

Table 1: Relative pharmacovigilance capacity of countries projected to host five or more higher-risk product launches (2012-2015)	
<i>Least Capacity</i>	
Bangladesh	<ul style="list-style-type: none"> • Not a member of the WHO International Drug Monitoring Program (IDMP) • Minimal or no capacity for PV *
Benin	<ul style="list-style-type: none"> • Joined IDMP in 2011 • Minimal or no capacity for PV*
Burkina Faso	<ul style="list-style-type: none"> • Joined IDMP in 2011 • Minimal or no capacity for PV*
Burundi	<ul style="list-style-type: none"> • Associate member of IDMP • Minimal or no capacity for PV*
Cambodia	<ul style="list-style-type: none"> • Joined IDMP in 2012 • Minimal or no capacity for PV**
Cameroon	<ul style="list-style-type: none"> • Joined IDMP in 2012 • Minimal or no capacity for PV*
Chad	<ul style="list-style-type: none"> • Not a member of IDMP
Congo Rep	<ul style="list-style-type: none"> • Not a member of IDMP
Eritrea	<ul style="list-style-type: none"> • Joined IDMP in 2012
Guinea-Bissau	<ul style="list-style-type: none"> • Associate member of IDMP • Minimal or no capacity for PV*
Lesotho	<ul style="list-style-type: none"> • Not a member of IDMP
Malawi	<ul style="list-style-type: none"> • Not a member of IDMP • Has minimal PV structures in place*
Myanmar	<ul style="list-style-type: none"> • Not a member of IDMP
Niger	<ul style="list-style-type: none"> • Joined IDMP in 2012 • Minimal or no capacity for PV*
São Tomé & Príncipe	<ul style="list-style-type: none"> • Not a member of IDMP
<i>Mid-range Capacity</i>	
Democratic Rep. of Congo	<ul style="list-style-type: none"> • Joined IDMP in 2010 • Has minimal PV structures in place*
Ghana	<ul style="list-style-type: none"> • Joined IDMP in 2001 • Has capacity to collect and evaluate safety data* • Very low ADR reporting rate***
Kenya	<ul style="list-style-type: none"> • Joined IDMP in 2010 • Has minimal PV structures in place*
Mozambique	<ul style="list-style-type: none"> • Joined IDMP in 2005 • Has minimal PV structures in place* • Very low ADR reporting rate***
Senegal	<ul style="list-style-type: none"> • Joined IDMP in 2009 • Has minimal PV structures in place* • Very low ADR reporting rate***
Sierra Leone	<ul style="list-style-type: none"> • Joined IDMP in 2008 • Has minimal PV structures in place*
Tanzania	<ul style="list-style-type: none"> • Joined IDMP in 1993

	<ul style="list-style-type: none"> • Has capacity to collect and evaluate safety data* • Very low ADR reporting rate***
Togo	<ul style="list-style-type: none"> • Joined IDMP in 2007 • Has minimal PV structures in place*
Zimbabwe	<ul style="list-style-type: none"> • Joined IDMP in 1998 • Has minimal PV structures in place* • Very low ADR reporting rate***
<i>Most Capacity</i>	
India	<ul style="list-style-type: none"> • Joined IDMP in 1998 • Has a defined PV program to detect, evaluate, and prevent medicine safety issues ****
Nigeria	<ul style="list-style-type: none"> • Joined IDMP in 2004 • Performing PV system to detect, evaluate, and prevent medicine safety issues*
Uganda	<ul style="list-style-type: none"> • Joined IDMP in 2007 • Performing PV system to detect, evaluate, and prevent medicine safety issues*
Vietnam	<ul style="list-style-type: none"> • Joined IDMP in 1999

* Strengthening Pharmaceutical Systems (SPS) Program. 2011. Safety of Medicines in Sub-Saharan Africa: Assessment of Pharmacovigilance Systems and their Performance. Submitted to the US Agency for International Development by the Strengthening Pharmaceutical Systems (SPS) Program. Arlington, VA: Management Sciences for Health.

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*** Defined as 5 or less ADR reports to Vigibase per million inhabitants. Aagard L, et al. Global Patterns of Adverse Drug Reactions over a Decade: Analyses of Spontaneous Reports to Vigibase. Drug Saf. 2012; 35 (12) 1171-1182.

**** For example see: http://www.cdsc.nic.in/pharmacovigilance_intro.htm; http://www.cdsc.nic.in/pharmacovigilance_intro.htm; <http://www.aiims.edu/aiims/departments/pharmacology/pvpi/pvmainfram.htm>

Table 2: Relative pharmacovigilance capacity of countries projected to host four or more higher-risk product launches (2016-2018)	
<i>Least Capacity</i>	
Bangladesh	<ul style="list-style-type: none"> • Not a member of the International Drug Monitoring Program (IDMP) • Minimal or no capacity for PV*
Benin	<ul style="list-style-type: none"> • Joined IDMP in 2011 • Minimal or no capacity for PV*
Burundi	<ul style="list-style-type: none"> • Associate member of IDMP • Minimal or no capacity for PV*
Cambodia	<ul style="list-style-type: none"> • Joined IDMP in 2012 • Minimal or no capacity for PV **
Gambia	<ul style="list-style-type: none"> • Associate member of IDMP • Minimal or no capacity for PV *
Malawi	<ul style="list-style-type: none"> • Not a member of IDMP • Has minimal PV structures in place*
Niger	<ul style="list-style-type: none"> • Joined IDMP in 2012 • Minimal or no capacity for PV*
Pakistan	<ul style="list-style-type: none"> • Associate member of IDMP
<i>Mid-range Capacity</i>	
Ethiopia	<ul style="list-style-type: none"> • Joined IDMP in 2008 • Has minimal PV structures in place* • Very low ADR reporting rate**
Kenya	<ul style="list-style-type: none"> • Joined IDMP in 2010 • Has minimal PV structures in place*
Mozambique	<ul style="list-style-type: none"> • Joined IDMP in 2005 • Has minimal PV structures in place* • Very low ADR reporting rate**
Rwanda	<ul style="list-style-type: none"> • Associate member of IDMP • Has minimal PV structures in place*
Sierra Leone	<ul style="list-style-type: none"> • Joined IDMP in 2008 • Has minimal PV structures in place*
Tanzania	<ul style="list-style-type: none"> • Joined IDMP in 1993 • Has capacity to collect and evaluate safety data* • Very low ADR reporting rate**
Zambia	<ul style="list-style-type: none"> • Joined IDMP in 2010 • Has minimal PV structures in place*
<i>Most Capacity</i>	
India	<ul style="list-style-type: none"> • Joined IDMP in 1998 • Has a defined PV program to detect, evaluate, and prevent medicine safety issues ****
Nigeria	<ul style="list-style-type: none"> • Joined IDMP in 2004 • Performing PV system to detect, evaluate, and prevent medicine safety issue*

* Strengthening Pharmaceutical Systems (SPS) Program. 2011. *Safety of Medicines in Sub-Saharan Africa: Assessment of Pharmacovigilance Systems and their Performance*. Submitted to the US Agency for International Development by the Strengthening Pharmaceutical Systems (SPS) Program. Arlington, VA: Management Sciences for Health

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**** For example see: http://www.cdsc.nic.in/pharmacovigilance_intro.htm; http://www.cdsc.nic.in/pharmacovigilance_intro.htm; <http://www.aiims.edu/aiims/departments/pharmacology/pvpi/pvmainfram.htm>

Table 3: Relative pharmacovigilance capacity of countries projected to host three or more higher-risk product launches (2019-2022)	
<i>Least Capacity</i>	
Cameroon	<ul style="list-style-type: none"> • Joined IDMP in 2012 • Minimal or no capacity for PV*
Comoros	<ul style="list-style-type: none"> • Not a member of IDMP
Congo Rep	<ul style="list-style-type: none"> • Not a member of IDMP
Korea DPR	<ul style="list-style-type: none"> • Not a member of IDMP
Madagascar	<ul style="list-style-type: none"> • Joined IDMP in 2009 • Minimal or no capacity for PV*
Mauritania	<ul style="list-style-type: none"> • Associate member of IDMP
Nepal	<ul style="list-style-type: none"> • Joined IDMP in 2006 • Has minimal or no PV structures in place** • Very low ADR reporting rate***
Sudan (presumably applies to both)	<ul style="list-style-type: none"> • Joined IDMP in 2008 • Minimal or no capacity for PV*
<i>Mid-range Capacity</i>	
Democratic Rep. of Congo	<ul style="list-style-type: none"> • Joined IDMP in 2010 • Has minimal PV structures in place*
Ethiopia	<ul style="list-style-type: none"> • Joined IDMP in 2008 • Has minimal PV structures in place* • Very low ADR reporting rate***
<i>Most Capacity</i>	
India	<ul style="list-style-type: none"> • Joined IDMP in 1998 • Has a defined PV program to detect, evaluate, and prevent medicine safety issues ****

* Strengthening Pharmaceutical Systems (SPS) Program. 2011. *Safety of Medicines in Sub-Saharan Africa: Assessment of Pharmacovigilance Systems and their Performance*. Submitted to the US Agency for International Development by the Strengthening Pharmaceutical Systems (SPS) Program. Arlington, VA: Management Sciences for Health

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Table 4. Guidance from US FDA for newly identified safety signals emerging from drug development, i.e., Phases I through III

Meaningful changes in previously identified adverse reactions (e.g., increased frequency or severity, outcome, specific at-risk populations)
Symptoms, signs, and laboratory evidence of newly and previously identified clinically significant toxicities, for example: hepatotoxicity, cardiovascular effects, including QT interval prolongation and results from thorough QT/QTc studies, bone marrow toxicity, pulmonary toxicity, renal toxicity, central nervous system toxicity, immunogenicity and hypersensitivity
Deaths that are an outcome of an adverse event
Study drug discontinuations because of adverse events, including abnormal laboratory values or investigations
Drug–drug and other interactions
Important nonclinical safety findings
Manufacturing issues that could affect risk
Lack of efficacy where this would place trial participants at risk
Any specific safety issues related to special populations, such as the elderly, children, patients with hepatic or renal impairment, or any other at-risk groups (e.g., slow or fast metabolizers)
Pregnancy and lactation exposure and outcomes
Safety findings arising from experience with long-term treatment
Evidence of clinically significant medication errors
Evidence of lack of patient compliance
Experience with overdose and its treatment
Occurrences of drug misuse and abuse
Any safety issues resulting from procedures required by the protocol (e.g., bronchoscopy, biopsy, central line insertion) or associated with the conduct or the design of a particular study (e.g., inadequate subject monitoring schedule, excessive period without active treatment) and
Potential impact of significant new safety issues identified with another drug in the same class

Glossary of Key Terms

Adverse event - 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. An appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product, which predicts hazard from future administration and warrants prevention or specific treatment, or alteration of the dosage regimen, or withdrawal of the product.

Adverse event of special interest - An adverse event of special interest (serious or non-serious) is one of scientific and medical concern specific to the sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor can be appropriate. Such an event might warrant further investigation in order to characterize and understand it. Depending on the nature of the event, rapid communication by the trial sponsor to other parties (e.g., regulators) might also be warranted. (Based on CIOMS VI).

Benefit-risk profile - Description or analysis of whether the therapeutic benefits of using a pharmaceutical product outweigh the risks involved. This balance can be different for certain groups of patients or for those with particular coexisting conditions/diseases.

Frequency of ADRs (from WHO-UMC) - In giving an estimate of the frequency of ADRs the following standard categories are recommended:

Very common* > 10%

Common (frequent) >1% and <10%

Uncommon (infrequent) >0.1% and < 1%

Rare >0.01% and <0.1%

Very rare <0.01%

Identified risk - An untoward occurrence for which there is adequate evidence of an association with the medicinal product of interest. (Volume 9A Rules Governing Medicinal Products in the EU). Examples of identified risks include:

- an adverse reaction adequately demonstrated in nonclinical studies and confirmed by clinical data.
- an adverse reaction observed in well-designed clinical trials or epidemiological studies for which the magnitude of the difference compared with the comparator group (placebo or active substance) on a parameter of interest suggests a causal relationship.
- an adverse reaction suggested by a number of well-documented spontaneous reports where causality is strongly supported by temporal relationship and biological plausibility, such as anaphylactic reactions or application site reactions.

Important identified risk; important potential risk - An identified risk or potential risk that could have an impact on the risk-benefit balance of the product or have implications for public health. (Volume 9A Rules Governing Medicinal Products in the EU).

New Chemical Entity (NCE) or New Molecular Entity - The product contains no active moiety that has been approved by a regulatory authority.

Pharmacoepidemiology - Study of the use and effects of drugs in large populations.

Pharmacovigilance - The science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem. This includes the use of pharmacoepidemiological studies.

Pharmacovigilance plan - A plan developed by a sponsor that is focused on detecting new safety risks and/or evaluating already identified safety risks. Specifically, a pharmacovigilance plan describes pharmacovigilance efforts above and beyond routine post-marketing spontaneous reporting, and is designed to enhance and expedite the sponsor's acquisition of safety information. Note: As used in the ICH document, a "pharmacovigilance plan" would be routinely developed (i.e., even when a sponsor does not anticipate that enhanced pharmacovigilance efforts are necessary). In contrast, as discussed above, FDA is only recommending that pharmacovigilance plans be developed when warranted by unusual safety risks.

Post-approval studies - A study conducted during the post-approval period, often under the terms of the approval to market the medicine. For example, a post-marketing surveillance study (PMS) is designed to obtain additional safety/efficacy data in approved indications, either in formal clinical studies or in noninterventional studies. A post-authorization safety study (PASS) aims specifically to identify or quantify a safety hazard related to an approved medicine.

Post-authorization safety study (PASS) - A pharmacoepidemiological study or a clinical trial carried out in accordance with the terms of the Marketing Authorization, with the aim of identifying or quantifying a safety hazard relating to an authorized medicinal product.

Potential risk - An untoward occurrence for which there is some basis for suspicion of an association with the medicinal product of interest but where this association has not been confirmed. (Volume 9A Rules Governing Medicinal Products in the EU). Examples of potential risks include:

- Nonclinical safety concerns that have not been observed or resolved in clinical studies
- Adverse events observed in clinical trials or epidemiological studies for which the magnitude of the difference, compared with the comparator group (placebo or active substance, or unexposed group), on the parameter of interest raises a suspicion of, but is not large enough to suggest, a causal relationship
- A signal arising from a spontaneous adverse reaction reporting system

- An event which is known to be associated with other products of the same class or which could be expected to occur based on the properties of the medicinal product

Registry - A registry is a list of patients presenting with the same characteristic(s). This characteristic can be a disease (disease registry), condition (pregnancy registry) or a specific exposure (drug registry). Both types of registries, which only differ by the type of patient data of interest, can collect information using standardized information in a prospective fashion.

Risk - The probability of an untoward outcome and the severity of the resultant harm associated with a medicine used under specified conditions in a defined population. (MHRA)

Risk management system - A set of pharmacovigilance activities and interventions designed to identify, characterize, prevent or minimize risks relating to medicinal products including the assessment of the effectiveness of those activities and interventions. (EMA)

Serious adverse event (SAE) - Any untoward medical occurrence that at any dose causes death, constitutes a life-threatening event, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity, or is a congenital anomaly/birth defect.

Signal: Information that arises from one or multiple sources (including observations and experiments), that suggests a new potentially causal association, or a new aspect of a known association, between an intervention and an event or set of related events, either adverse or beneficial, that is judged to be of sufficient likelihood to justify further action to verify. (ICH)