Safety of medicines

“Project 3-S”: Smart Safety Surveillance for priority medical products

Access to medicines and vaccines in low- and middle-income countries (LMICs) has improved in the past two decades. However there has not been a proportionate improvement in pharmacovigilance infrastructure and activities to monitor adverse events and address safety issues. This is of particular concern as there is a sizeable pipeline of novel products to be introduced in LMICs. These products are developed in well-resourced settings, with baseline safety data that may not be entirely applicable to the population and context of target countries.

Safety monitoring of medicines is essential to protect people from harm. The lack of functional pharmacovigilance structures could become a barrier to the introduction of these products to some LMICs and could seriously undermine the treatment options available to patients. A new project proposes to strengthen pharmacovigilance capacity in LMICs and, in the long-term, establish end-to-end safety surveillance of products from their clinical development to the post-market stages. In its current phase the project focuses on selected medicines and vaccines that will be introduced in the next few years.

Safety monitoring of medicines

Although rigorous clinical trials are conducted during medicines development, a complete set of safety data only becomes known once a product has been on the market for a long time. Continued safety monitoring in real world settings, where medicines are used together with other products, among different patient populations and in patients with multiple illnesses, is therefore critically important.

At the global level, pharmacovigilance is conducted through the WHO Programme for International Drug Monitoring. Data are collected in VigiBase, the WHO global pharmacovigilance database of adverse events. Set up nearly five decades ago, this database is managed and maintained by the WHO Collaborating Centre in Sweden, also known as the Uppsala Monitoring Centre (UMC). Participation by WHO Member States has increased steadily, and as of November 2017, VigiBase has received more than 16 million individual case safety reports from 127 countries worldwide. The VigiBase data comply with the highest

This article is based on information contributed by the WHO Safety and Vigilance (SAV) Team and the Bill & Melinda Gates Foundation, with Monika Zweygarth as editor.
Challenges in LMICs

Weak regulatory systems
Although pharmacovigilance programmes have been created in many resource-limited countries since the 1990s they remain understaffed, underfunded and often without strong legal or regulatory provisions. Data from WHO and its collaborating centres suggest that only about one third of sub-Saharan African countries meet the WHO-defined minimum pharmacovigilance requirements, and many lack a standardized data management system.

As there is limited enforcement and awareness of pharmacovigilance in LMICs, few reports are made by health care providers and patients, and most of them lack clinically important information that could support causality assessment. And on the part of industry there is often little emphasis on local risk management plans in developing markets, given the limited pharmacovigilance requirements.

As a result of these weaknesses, there is substantial underreporting of suspected adverse events in LMICs, and very few regulatory decisions on medicines safety in LMICs are based on local data. These shortcomings are also reflected in the reports made to VigiBase: Sub-Saharan African countries contribute less than 1% of all individual case safety reports (ICSR).

Box 1: Project Triple-S — Core approaches

- **Pilot products**: Adopt a stepwise approach with an initial pilot for three new products (two medicines and one vaccine)
- **Leverage available resources** from partners: WHO International Drug Monitoring Programme, Global Vaccine Safety Initiative, Uppsala Monitoring Centre and other WHO collaborating centres, national pharmacovigilance centres and others
- **Industry partnership**: Develop integrated plans that include key marketing authorization holders
- **Holistic country plan**: Develop a holistic plan for pharmacovigilance as part of medicines regulation in the defined countries
- **Collaboration**: Liaise with other ongoing initiatives, such as the African Medicines Regulatory Harmonization (AMRH) initiative
- **Progressive development**: Build pharmacovigilance infrastructure progressively, moving from minimum to mid-range and advanced capacity.
**Complex health care systems**

In most resource-limited countries the public and private health care systems are complemented by donor-funded public health programmes to fight high-burden diseases such as HIV, tuberculosis and malaria, to address neglected diseases, or to increase immunization coverage. Medical products dispensed in these programmes often account for the majority of pharmaceuticals used in resource-limited settings. They are often approved through fast-track mechanisms and scaled up rapidly, despite little experience with their safety in target countries.

The pharmacovigilance needs in the treatment of specific diseases have provided an opportunity to introduce pharmacovigilance systems into additional resource-limited countries. Between 2000 and 2010 the number of sub-Saharan African countries with functional pharmacovigilance centres increased from less than 10 to well over 20. In addition, donors have been supporting projects to monitor the safety and safe use of medicines in their programmes. However, where such projects exist they tend to have limited objectives and do not necessarily collaborate with national pharmacovigilance centres.\(^{(5)}\)

**Product pipeline for LMICs**

The gaps in pharmacovigilance are problematic because an increasing pipeline of novel products designed for introduction in LMICs. Some products are under development for use exclusively in LMICs to treat neglected diseases such as Ebola, dengue, malaria, schistosomiasis, leishmaniasis or human African trypanosomiasis. Others are intended to fight diseases that affect countries globally, such as multi-drug resistant tuberculosis, hepatitis C infection or human papillomavirus. And yet others may need to be developed rapidly in response to emergencies, as happened with Ebola vaccines during the West Africa epidemic.

However, these products are mostly being developed in well-resourced settings that do not reflect the social, economic, epidemiological or health conditions of LMICs. As a result, limited baseline safety data are available at the time of their approval for use in LMICs, making safety monitoring critical.

**Project 3-S**

**Smart safety surveillance**

To support LMICs in the introduction of new products, the WHO Safety and Vigilance (SAV) Team has initiated a project to optimize post-marketing surveillance of priority medicines and vaccines in LMICs. The project will use a smart safety surveillance (“3-S”) approach that initially focuses on selected priority products to be introduced in LMICs. Regulators will be supported in identifying, assessing, and adequately managing the risks associated with these products. As safety data will be generated on specific products in parallel with their first use, national pharmacovigilance systems and competence will be strengthened to enable safety monitoring of all products in the long-term.

A new partnership between WHO and the Bill & Melinda Gates Foundation has been established to advance this work. Project 3-S proposes to strengthen, expand and streamline pharmacovigilance systems in LMICs. Its core approaches are designed to identify the strategies that work well, and scale them up to additional countries and products (Box 1).
Pilot products
In its pilot phase Project 3-S will build surveillance systems for three pilot products. A shortlist of products has been drawn up taking into consideration emerging product launches, use of accelerated or conditional approval, adverse events identified in clinical development, public health impact, and exclusive target populations.

Project 3-S will be piloted in four to six countries of varying pharmacovigilance readiness. Surveys have been completed in 3 countries and are under way in another 4 to evaluate the successes and challenges in pharmacovigilance management. The pilot phase will serve to understand the types of countries and systems that will benefit the most from external support. If proven, the concept of Project 3-S will be extended to additional countries and regions.

Holistic country plan
Pharmacovigilance strengthening must be integrated with broader initiatives to strengthen regulatory systems. The ultimate goal of Project 3-S is to establish end-to-end pharmacovigilance systems, with timely and adequate reporting of adverse drug reactions, followed by timely review and any needed regulatory action. A holistic plan for pharmacovigilance will be developed in each country, covering: (1) policy, law and regulation, (2) system, structure and stakeholder coordination, (3) signal generation and data management, (4) risk assessment and evaluation, and (5) risk management, communication and allocation of commensurate resources.

Leverage available resources
To ensure effective safety monitoring in line with international standards, use will be made of guidance, infrastructure, expertise and resources available from global partners (Box 1).

The importance of good alignment between medicines and vaccines vigilance is well recognized within Project 3-S. The new CIOMS Guide to Active Vaccine Safety Surveillance (6) provides valuable best practice guidance for developing pharmacovigilance and aligning the principles for vaccines and medicines. The two relevant WHO-convened global advisory committees will be represented in the Project Advisory Group and will provide advice on research protocols, methodologies, review data, and guide national investments and initiatives. The WHO public health programmes and the Prequalification Team can support the assessment of baseline product safety data in collaboration with regulators and industry.

To prepare the ground for Project 3-S, a core curriculum has been developed to train health professionals in quality reporting and analysis of adverse events in resource-limited settings. An inaugural training workshop took place in Mombasa, Kenya, in Q4 2016; representatives from 12 African countries attended. Training workshops of this nature will take place regularly going forward.

Progressive development
The project’s success will depend on the target countries’ ability to adopt and implement pharmacovigilance. An assessment of the potential target countries, and of relevant local stakeholders will be critical. WHO has coordinated the development of an up-to-date global set of indicators to assess pharmacovigilance readiness within the context of Project 3-S. These indicators are drawn from the 2015 WHO pharmacovigilance indicators (7) and other recognized global pharmacovigilance
and assessment tools. They will be used to assess the pharmacovigilance infrastructure, competence, capacity and gaps in target countries against global standards. As the project progresses, pharmacovigilance infrastructure will be expanded to build more advanced safety monitoring and risk minimization functions into the national regulatory systems. In this phase the CIOMS Working Group IX report Practical Approaches to Risk Minimisation for Medicinal Products (8) provides real life examples and can serve as a practical risk management toolkit.

**Collaboration**

An increasing number of organizations have become involved in regulatory systems strengthening. WHO is in the process of establishing a “Coalition of Interested Partners” framework to achieve better coordination, efficiency, outcomes and sustainability of the different partners’ efforts in Member States or regions.1 Project 3-S will serve as a pathfinder pilot for this approach in the area of pharmacovigilance. Work-sharing and joint activities in ongoing initiatives such as the African Medicines Regulatory Harmonization (AMRH) and the African Vaccines Regulatory Forum (AVAREF) could create significant synergy and enhance impact. For example, a product could be monitored intensively in one or two countries and the data made available to neighbouring countries, or regional risk-assessment committees could jointly review data on priority products for mutual learning and regional decisions.

To sustain the impact of Project 3-S beyond the pilot WHO has engaged with external partners who can provide technical expertise, financial investment or coordination capabilities. Key stakeholder meetings were held in October 2015, March 2016 and January 2017 to introduce the initiative, gain endorsement of the core objectives and approach, and ensure alliances are formed going forward. Major organizations have expressed their commitment to support Project 3-S, and the ongoing and planned contributions of each partner in different areas have been mapped.

**Conclusion**

There is growing international attention to strengthening pharmacovigilance globally. Members of the WHO advisory committee on safety of medicinal products have commented that Project 3-S with its focus on priority products will be a “game-changer” which may well impact future product launches.3 Encouragingly, there are examples of national systems that are stepping up to the need for safety monitoring of new medicines. In India a detailed procedure has been established for recording and reporting adverse events observed with bedaquiline at designated treatment sites for multidrug-resistant tuberculosis, and data are transferred automatically between the tuberculosis programme and the national pharmacovigilance database.3 The pharmacovigilance structures that now exist in some LMICs, and the strong interest that these countries demonstrate in improving their systems and capacity, could facilitate the success of Project 3-S both nationally and in collaborative or regional settings.

It is hoped that by involving the relevant national authority, and through

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1 The approach was endorsed in the 17th International Conference of Drug Regulatory Authorities (ICDRA) recommendation to “Incorporate an innovative and more coordinated approach to regulatory systems strengthening such as coalition of interested partners and centres of excellence”.(9)
integration in the national medicines policy, pharmacovigilance will become the norm for medical products in LMICs as part of each authority’s regulatory mandate. Uptake and application of the key principles for strengthening pharmacovigilance systems in additional regions will be an important measure of success. Ultimately, such systems should enable regulators to respond quickly and adequately to potential safety risks with all products throughout their life cycle, ensuring that patients can rely on their health services to provide them with safe vaccines and medicines.

References


2 WHO Minimum Requirements for a Functional Pharmacovigilance System. 2010.


7 2015 WHO Pharmacovigilance indicators.


Further reading: