Q&A on Pharmacovigilance Requirements

Q: Would patients be safe to use the products if local authorities proceed with local quality tests and package adaptation?

One of the most important aspects of ensuring product safety is a robust pharmacovigilance (PV) program. Complete and timely reporting of adverse events is a legal responsibility of the product registration holder in all Latin American countries. Therefore, assuring product safety is not simply a matter of adapting the packaging, and including quality testing at the point of product importation, it involves complying with much more complex requirements that only suppliers with a local infrastructure (either their own or that of their distributor) can comply with.

Some of these requirements include:

- Providing a Risk Management Plan at the time of product registration
- Providing Periodic Benefit Risk Evaluation Report reports (PBRER) to local authorities as defined by local regulation
- Timely reporting of adverse events and safety issues to local health authorities
- Up-dating risk management plans along the product's lifecycle
- Adapting product labeling and insert to improve patient and medical information and mitigate side-effects according to information received by product reporting
- Demonstrate capacity and readiness to conduct adverse event reporting and provide patient and healthcare professional support by passing periodic and random audits
- Local infrastructure (either of the manufacturer or their authorized distributor)provides a framework for an early warning system and detection of unexpected adverse reactions as the first line of protection for patients

None of these requirements can be fulfilled by a supplier without appropriate local infrastructure.

The importance of local infrastructure for PV is clear in these examples from Brazil and from Argentina:

Brazil:

- Brazil has a decentralized PV network composed by Federal (ANVISA), State and Municipal Surveillance Agencies. The largest State surveillance agency is the one of the State of Sao Paulo (CVS/SP) where most of pharmaceutical market authorization holders (MAH) are located.
- All adverse events of MAH based in the state of Sao Paulo must be reported to CVS/SP and all others are reported to ANVISA (the two databanks are not yet

connected, the information exchange is via reports).

- Data from the CVS/SP demonstrates the critical role that reporting to the MAH has in capturing adverse event reporting and/or identifying safety issue in Brazil*:
    - Of a total of 31 Thousand cases of adverse events** reported to CVS/SP 83% were reported by MAH***
    - Only 17% were reported by hospitals, clinics, pharmacies etc.
- During the same period, ANVISA received directly from other states in Brazil 10,586 Adverse Event Reporting but does not report data by reporting source. ****
- If ANVISA reporting source is similar that of Sao Paulo's, **we estimate that if MAHs did not have a structure to report adverse events in the country, approximately 41,500 cases of Serious Adverse Events, Adverse Reactions and Unexpected Adverse Reactions would go unreported in Brazil every year**. This highlights the importance of PV processes to be carried out by locally established suppliers.

* Periweb data presented by CVS, Adalton G. Ribeiro, Technical Director CVS/SP October 3rd, 2018
**Serious Adverse Events, Adverse Reactions and Unexpected Adverse Reactions
*** 31 thousand reports from January 1st 2018 to October 2nd 2018
****ANVISA, Vigimed Report number 5, 2018

Argentina:

- The last report published by ANMAT* indicates that the *Sistema Nacional de Farmacovigilancia (SNFVG)* received 12.306 notifications of adverse reactions in Argentina in 2017:
    - 94,3% of all the adverse events reported in Argentina were captured by market authorization holders
- This indicated that **if MAHs did not have a structure to report adverse events in the country, approximately 11,600 cases of Adverse Events, would go unreported in Argentina every year**.

* Departamento de Farmacovigilancia, ANMAT, Reporte Anual 2016

The need for local infrastructure is so relevant that most countries in the region require a local product responsible (healthcare professional) and in many cases, the person needs to be physically located in the country:

Country	Regulation/Law that requires local product responsible
Brazil	RDC04/2009
Chile	Norma 140/2012

Argentina	2438/2000
Paraguay	Documento 3/2016
Bolivia	Documento 210/2011
Peru	Ministerial Resolution N° 539-2016-MINSA

*Uruguay, Panama, Colombia and Mexico all require a responsible pharmacovigilance professional, but the regulation does not specify the need to be located in the country.

The responsibility of the MAH on monitoring pharmaceuticals in the market is also emphasized by **WHO's guidance on drug safety for public health programs**:

"[holders] are legally responsible for the safety and effectiveness of medicines while the product is available in the marketplace. […] They also have a duty towards assessing the effectiveness and safety of a PHP [public health program] and the benefits to patients. ***They should report adverse reactions both to the national pharmacovigilance centre (or in the absence of such to the MRA) or PHP and, in countries with no MRA they should also report to WHO through the disease control PHP"***

PAHO has also highlighted the critical importance that PV has for Latin America. *According to* ***PAHO's Good Pharmacovigilance Practices for the Americas****:*

"Health needs and medicine usage varies widely from country to country. There are many reasons for this, among them economics, ethnicity, culture, the burden of disease, and diet, as well as a country's development level and medicine regulatory system. As a result, decisions concerning safety and efficacy must be considered in the specific context of each country. ***Thus, monitoring of the safety and efficacy of medicines must be a public health priority."***

Q: For decades, PAHO has procured vaccines at a centralized level for LATAM and almost all vaccines and ARV products are currently procured via PAHO. PAHO has a quality control and adverse event reporting system for the products, why would they not work for all products?

(needs validation)

- PAHO's pharmacovigilance relies on the WHO's individual case safety report (ICSR) database – Vigibase. Vigibase collects reports informed to the WHO Collaborating Centre for International Drug Monitoring, Uppsala, Sweden (UMC). This system, in turn, relies on the reports provided by national centers and other established regulatory authorities. These, in turn, rely heavily (as seen in the Brazilian and Argentinean cases above) on local reporting by Market Authorization Holders.
- **Without MAH's pharmacovigilance infrastructure and reporting to local authorities in Latin America the vast majority of adverse events in Latin**

America would go unidentified and would never make to the WHO database. If products are imported via international agencies without properly following local PV requirements, the entire PV system is jeopardized.