FACT SHEET 5

PHARMACOVIGILANCE:
MONITORING AND TRACEABILITY ACROSS THE SYSTEM

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PHARMACOVIGILANCE

Pharmacovigilance – the monitoring of adverse drug reactions (ADRs) in medicines used by patients in clinical practice – is critical for all medicines, including biologics. Unfortunately, investment in pharmacovigilance systems is insufficient worldwide, and this is particularly true for LMICs. In many countries however, health providers as well as patient groups are engaging with their governments and regulatory authorities to improve pharmacovigilance systems and helping to find pragmatic solutions that are both appropriate and feasible in lower-resourced environments.

The strengthening of pharmacovigilance systems is a priority worldwide – with implications for all medicines, not just biologics.

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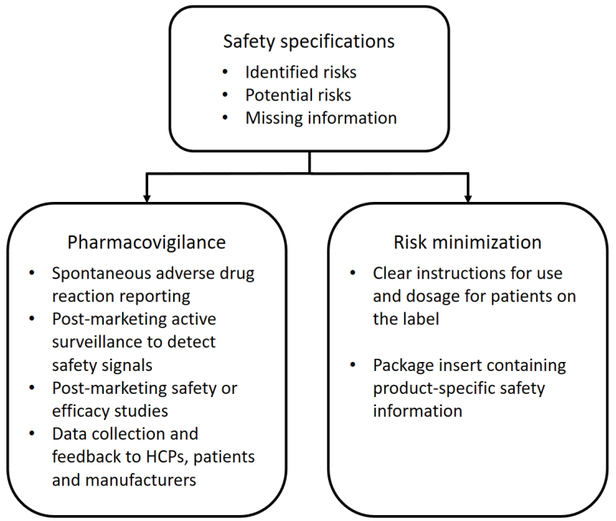
Pharmacovigilance systems are a critical part of the risk management plan for any medicine – including biologics (Figure 1). They should include accessible and transparent reporting protocols for doctors and patients, reliable databases that collate information from all relevant health care settings and send appropriate signals to NRAs and health professionals as appropriate. Clear and effective protocols that guide healthcare professionals through the process of reporting an adverse drug reaction are also critical to establish confidence in healthcare systems and compliance with established regulations. (**Figure 2**). Pharmacovigilance data are not only key to monitor ADRs in patients, they are also used to identify diagnostic features, syndromes or pathogenic mechanisms[1], and also help manufacturers improve their safety and efficacy.

RISK MANAGEMENT PLAN

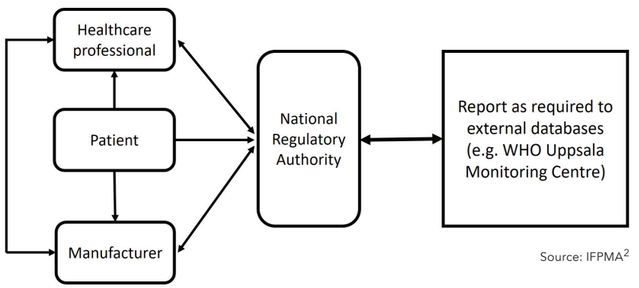
Figure 1.



Source: IFPMA[2]

REPORTING PATHWAY OF ADR FROM REPORTER TO FINAL DATABASE

Figure 2.



Source: IFPMA[2]

Pharmacovigilance is key to safe and effective use of all biologics. In evaluating a drug, regulators must balance the benefits against harms. Not all of the potential positive or negative effects of a drug, especially a biologic, can be known when applying for a market authorization. That is the primary reason why systems and procedures to monitor drug effects are essential to assure safe and appropriate use of biologic medicines. Traditionally, pharmacovigilance was mostly concerned with collecting data on ADRs, but in regards to biologics, which can potentially trigger very different responses in different populations, efficacy is also an important factor to monitor.[3] To those ends, the WHO guidelines recommend that manufacturers of all biologics submit to the NRA a plan for monitoring the 'real-world' performance of their product. The NRA, in response, must ensure the manufacturers comply with the submitted plan once the medicine is in clinical use.[4 5]

The need to strengthen pharmacovigilance systems is particularly acute in many LMICs.[6]

Despite the importance of pharmacovigilance, under-reporting of ADRs is a critical issue in all countries (**Table 1**). A recent global survey from WHO across 55 LMICs found only 23 countries allocated a specific budget for pharmacovigilance, and in over 80% of the countries surveyed, the total number of pharmacovigilance staff was less than ten per country. Additionally, national pharmacovigilance staff in LMICs often require further technical training and support as well as empowering regulations to enable them to carry out rigorous pharmacovigilance.[7]

Emerging strategies such as the African cross-border pharmacovigilance work sharing initiative can play a critical role in pooling information and resources to strengthen pharmacovigilance efforts.[8] Other noteworthy efforts include the Danish Action Plan for better monitoring of biologics (**Case study 1**), where the creation of a transparent pharmacovigilance system has resulted in improved monitoring of the safety and efficacy of biologics as well as increased public confidence in biosimilars.

WHO guidelines recommend that all ADRs for biologics including biosimilars be documented and reported up to the national regulatory agency to capture a full picture of the quality, safety, and efficacy of each product.

VARIATION IN THE STATUS OF ADR REPORTING IN COUNTRIES AROUND THE WORLD

Table 1.

Country	Number of Individual Case Safety Reports per million inhabitants per year (2011-2016)
Brazil	2
Colombia	124
Mexico	48
Peru	171
India	30
Iran	29
Thailand	427
Ghana	12
South Africa	58
United States	2151
South Korea	2794
Singapore	3804
Canada	1121
Switzerland	834
Netherlands	811
Denmark	789
Australia	497
United Kingdom	452
Germany	407

This table reflects the number of reports submitted to VigiBase®, acquired through correspondence with the WHO Collaborating Center for International Drug Monitoring (Uppsala Monitoring Centre). This does not always reflect the number of reports actually received by the national centre for different reasons such as technical problems, or limited human or financial resources in each member country.

CASE STUDY 2 / Salud Derechos y Justicia (SDJ), Mexico

The greatest challenge to ensure access and safety of biologics including biosimilars in Mexico is the fragmented nature of the healthcare system. The Mexican public healthcare system has multiple institutions (e.g. IMSS, ISSSTE, PEMEX, Armed Forces), who have their own rules and regulations. It implies they all have their own rules regarding prescription, switching, and reimbursement decisions.

SDJ has been working with individual patients to improve pharmacovigilance by generating robust field evidence and leveraging the body of evidence to discuss patients' ADR concerns with the healthcare institutions. They receive direct ADR reports from individual patients, and they have also placed key patient informants in different regions to collect ADR reports from all parts of Mexico. With the ground-level evidence, SDJ initiates dialogues with the local hospitals and institutions on ensuring access to treatment – for example, identifying and fighting supply disruptions – as well as safeguarding the quality of treatment patients receive.

SDJ traces the source of ADR by cross-comparing a patient's medical records to the public domain government data.

Because the reimbursement code prescription practice (based on the INN) has been common across Mexico and hinders pinpointing the source of ADR, SDJ leverages the freedom of information act to request viewing of drug procurement contracts between institutions and pharmaceutical companies. While this method is not 100% precise, it does provide a higher precision of ADR investigation compared to the readily available information in patients' medical records alone. With this transparent process of triangulation, the public health institutions and ministry officials are open to engage in dialogues with SDJ.

CASE STUDY 3 / Associação Brasileira de Linfoma e Leucemia (ABRALE), Brazil

ABRALE, the Brazilian Association of Lymphoma and Leukaemia Patients, approaches the issues of biologics through both patient education and monitoring of implementation of government plans.

Patient education: In Brazil, ADR reporting is reserved for health professionals in practice, therefore it is difficult for ordinary patients to access the pharmacovigilance system. ABRALE advises patients to contact them for any potential signs of ADR, so that health professionals who are with ABRALE can report such potential ADRs on behalf of the patients.

ABRALE tasks its professional committees (comprised of qualified persons in medical, nursing, pharmacy, and legal affairs) with providing detailed education to patients on pharmacovigilance. The curriculum covers continuing education on drug-specific or treatment information as well as the importance of ADR reporting to support national pharmacovigilance activities.

Enabling and empowering patients to directly report ADRs may contribute to more comprehensive pharmacovigilance efforts and improving reporting overall.

Despite the limitations above direct patient reporting of ADRs could add value to pharmacovigilance efforts, especially by improving our understanding of how biologics work in real-life settings.[19 23] Studies from the UK and the Netherlands, for example, found that direct patient reports strengthened safety signal detection, rather than hampering it with 'distracting noise' from more traditional, physician-led ADR reporting.[23] In Mexico, health authorities have implemented a user-friendly, web-based direct ADR reporting system for patients [25] and health professionals.[26] This system was designed with the input from various patient organisations and other relevant stakeholders. It is expected to contribute to building consolidated pharmacovigilance database in conjunction with the recent pharmacovigilance reform in 2015,[27] which reflected input from patient organisations.[28]

Beyond direct reporting systems, patient groups may play a critical role in improving pharmacovigilance.

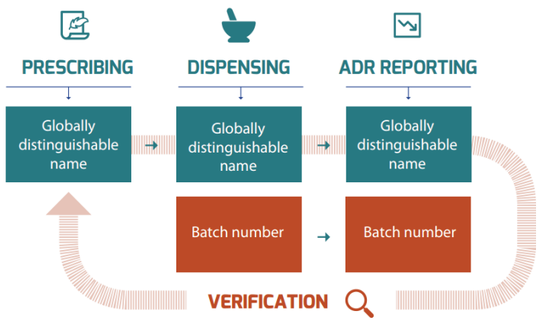
Patient groups in many countries have led significant efforts to engage the government, regulatory authorities and other stakeholders in improving the effectiveness and transparency of pharmacovigilance systems for biologics. Two case studies of such efforts in Mexico and Brazil may be found below (**Case studies 2 and 3**).

These approaches have helped to facilitate a constructive dialogue with the government on equal footing, and to enable a process to acknowledge, identify, and approach deeper systematic issues of drug safety. These initiatives demonstrate the power of patient groups not only to contribute to building more sustainable and powerful regulatory frameworks, but the importance of engaging them in these developments to ensure that the interests of patients are central to any reforms and proposals.

FULL TRACEABILITY THROUGHOUT THE PRESCRIBING,DISPENSING AND ADR REPORTING CHAIN

Figure 3.

Accurate identification of biotherapeutics or manufactured batch is one pillar of a good pharmacovigilance (PV) system.



CASE STUDY 1 / The Danish Action Plan for better monitoring of biologics including biosimilars (Handlingsplan om bedre overvågning af biologiske lægemidler, biosimilære lægemidler og vacciner 2015-2016).

The post-marketing monitoring of infliximab in Denmark illustrates a multi-stakeholder dialogue to facilitate an evidence-building solution. The Danish Council for the Use of Expensive Hospital Medicines (RADS) chose to purchase an infliximab biosimilar over its reference biologic, because both medicines have been shown to be equivalent. However, patients and physicians did not feel comfortable with it. In response, the Danish Ministry of Health launched the Action Plan on Better Monitoring of Biologics, Biosimilars and Vaccines 2015-2016* in September 2015.[9]

The new action plan focused on signal detection – finding new causal relationships between an adverse event and a medicine[10] – at the product level.[10] It also focused on educating health professionals on the importance of product-specific traceability for all biologics, for example reporting by the non-proprietary name, brand name, *and* batch number. It also raised awareness on biosimilars among patients, it also encouraged implementing IT solutions to ensure easy ADR reporting for biologics including biosimilars for hospitals and general practice clinics.[10 11]

From IFPMA[2] the results of the action plan are too early to be conclusive, but all stakeholders viewed the pilot results positively.[12] With the action plan, the Danish Ministry of Health hopes to help patients feel reassured; help doctors explain biosimilarity to patients; and strengthen the national pharmacovigilance system to meet the special needs of all biologics, including biosimilars.

The consistent use of product-specific identifiers is needed for all biologics to ensure traceability of any reported ADR to a specific biologic or biosimilar product.[12]

A key shortcoming of most established pharmacovigilance systems is that they do not accommodate product-specific traceability for biologics.[13] The WHO guidelines recommend that all biologics, including biosimilars, should be prescribed with not only the INN but also with brand names[12] in order to trace any ADR to a specific biologic or biosimilar product.

The all-too-common practice of prescribing medicines only by the non-proprietary name, combined with tender procurement and reimbursement practices that are solely based on the non-proprietary name hinders capabilities to trace ADRs back to specific medicines. These practices, typically developed to facilitate generic substitution of small-molecule medicines, are not only inappropriate but create potentially dangerous situations when extended to biologic medicines. The inability to distinguish among biologics, which share the same non-proprietary name but come from different manufacturers, hinder a full safety investigation in the case of an ADR.[14] To this end, it is also important to have a record of the batch number of any biologic dispensed to a patient in order to trace back not only the manufacturer but also specific batch that caused the ADR.[14]

> There are 20 different brands of epoetin in Thailand with a high incidence of adverse events, but the non-proprietary name mentions only alfa or beta forms, and the current pharmacovigilance system does not indicate any product-specific information, making it very difficult to collect data and investigate adverse events linked to a particular epoetin product. Doctors are aware of this issue, but the current system requires only the non-proprietary name to be written in, with the brand name optional, therefore there are no incentives for doctors to disclose which brand of epoetin they have used for their patients.
>
> Krisana Winitthumkul, Roche – Thailand

UNFORTUNATELY, THERE IS CURRENTLY NO INTERNATIONAL GUIDANCE ON APPROPRIATE NAMING SYSTEMS FOR BIOSIMILARS.

Guidance on the use of specific INNs for biosimilars is still in development at WHO.[15 16] Recent proposals from the INN Expert Group to WHO, at the request of various medicines regulatory authorities, recommend adding a random alphabetic code to the existing INN of all biologic medicines. The purpose of this additional identification element is to minimise errors in "prescription, dispensing, pharmacovigilance and international transfer of prescriptions."[16] The US Food and Drug Administration has also proposed a unique "randomly generated" suffix system for all biologics including biosimilars.[17]

Some very promising efforts to improve the traceability of biologics have been initiated by public health institutions and regulatory authorities, for example, those in Mexico and parts of Africa.

> COFEPRIS [the Mexican NRA] has been actively promoting the responsibility among all stakeholders to report all adverse events with high quality data. For example, COFEPRIS has been encouraging physicians in the national health institutions to use the 3-code reimbursement code, non-proprietary name, and brand name when prescribing all biologics and reporting adverse events. This effort reinforces the message from WHO about the value of having a consolidated pharmacovigilance system and traceable data in place. Now, the continuity of biologics history can be complete, from prescription to post-marketing ADR reporting.
>
> **Fernando Fon, the Mexican Association of Pharmaceutical Research Industries (AMIIF) – Mexico**

> The most innovative part of the (future) African Medicines Agency strategy is using mobile technology and new labelling technology to trace medicines, particularly batch numbers, via a simple text message. The penetration of mobile phones into rural setting is high, and it makes this vision feasible. It should be followed with a requisite education programme for community health workers and other lay health support staff, in addition to educating health professionals.
>
> **Kawaldip Sehmi, the International Alliance of Patients' Organizations**

Effective pharmacovigilance systems rely on health professionals as well as patients to identify and report any ADRs they observe.

Yet under-reporting by both health professionals and patients is a chronic problem, particularly in LMICs where pharmacovigilance systems are often poorly resourced.[18] Under-reporting by health professionals may occur for many reasons. Physicians may lack the time to pinpoint the source of ADR among patients with multiple medications – especially when they have heavy clinical workloads.[19] In countries where pharmacovigilance systems are in their early development stages, health professionals may feel discouraged by lack of clarity in the reporting systems,[20] lack of prompt feedback from NRAs and lack of resources devoted to pharmacovigilance.[21] In some cases, depending on the local culture, physicians may also fear that reporting an ADR could result in losing credibility and being perceived as someone who prescribes harmful medicines.[22]

Under-reporting by health professionals may also stem from the fact that they view ADRs differently from patients – a fact substantiated in published literature.[22-24] Typically, patients prioritise ADRs based on the impact on their quality of life.[23] Doctors, by contrast, may view the need to report ADRs differently. For example, a mild, persistent rash may have a negative long-term impact on a patient's quality of life, but doctors may not consider it 'serious' enough to report through the

Just as under-reporting is an issue with health professionals, many patients may not have sufficient information, knowledge or confidence to report ADRs they may be experiencing.

Many patients may still be unaware of how to recognise ADRs and how to report them.[19] In some cases, direct reporting channels for patients to report ADRs to the NRA or manufacturer may not be easily accessible to patients.[19] Patients may not know how to use the reporting channel with confidence. In LMICs, there may be additional challenges with illiterate or poorly-educated patients. These patients may not even know with certainty what medicines they are taking,[22] and therefore may find it difficult to articulate with precision the symptoms and timing of their ADR to their doctor.

> The quality of health services is a great struggle for physicians who work in public medical institutions. Their main concern is that they do not have a say on what is available at the pharmacy. Even though the regulations are rigorous for safety and efficacy, they are difficult to implement. We are starting with strengthening pharmacovigilance. We need to encourage health professionals and patients to report adverse events more.
>
> **Carlos Castro, Asociación Ale - Mexico**

> Although patients should be able to report ADRs straight to the Central Drugs Standard Control Organization, in reality it is inaccessible. Pharmacovigilance is very important but absent in practice, because patients and even many of the patient organisations do not know where to go to report ADR and raise safety concerns.
>
> **Rubby Chawla, the Indian Patients Society for Primary Immunodeficiency - India**