



IFPMA

Pharmacovigilance of biotherapeutic medicines:

*Identifying global case studies
illustrating successes and challenges*

Summary report

JUNE/2016





Learn more and stay connected

www.ifpma.org

Chemin des Mines 9

P.O. Box 195

1211 Geneva 20

Switzerland

Designed by ACW, London

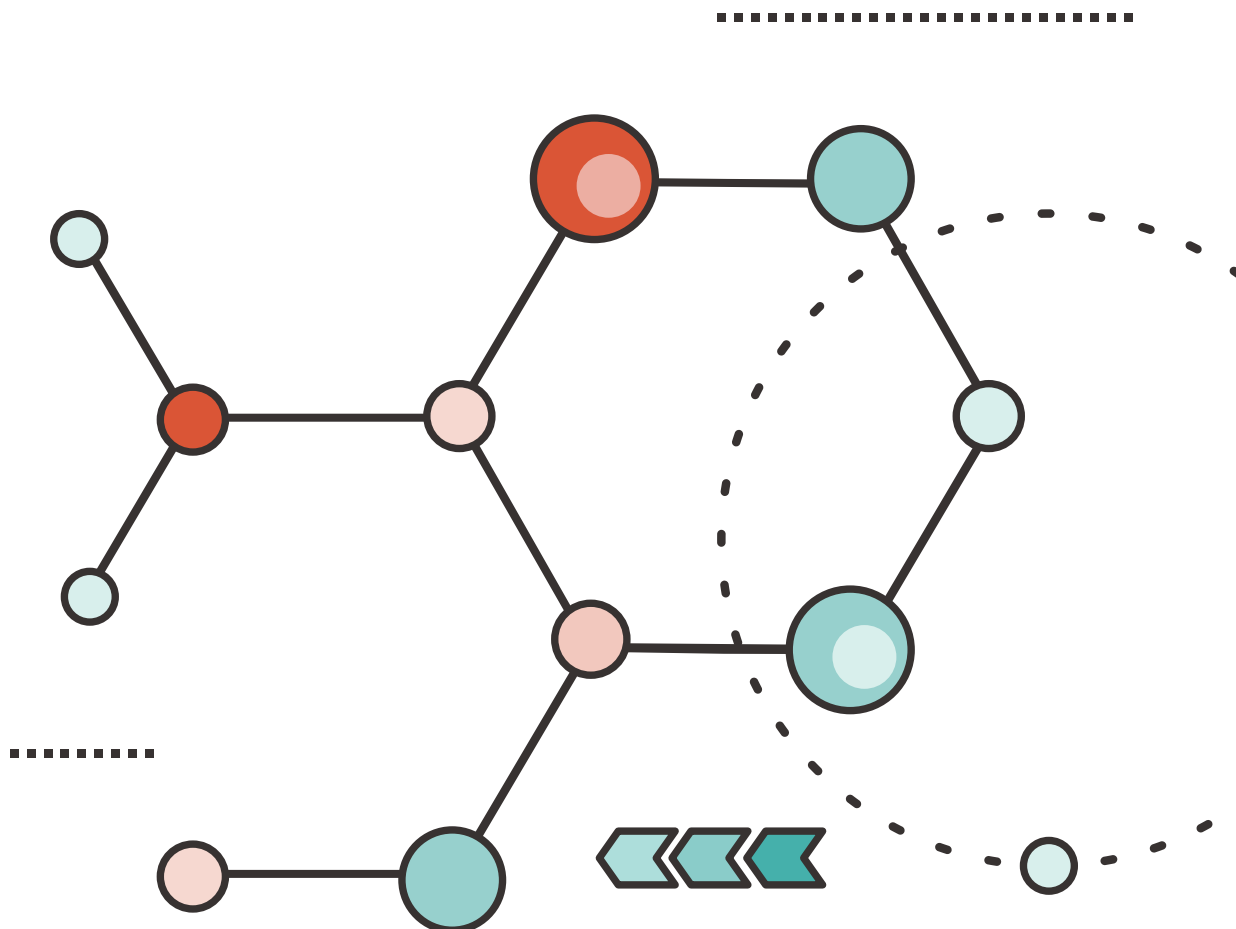
www.acw.uk.com

Pharmacovigilance of biotherapeutic medicines:

*Identifying global case studies
illustrating successes and challenges*

Summary report

JUNE/2016



Index



5

Foreword

14

Biotherapeutic Medicine
Pharmacovigilance Strategies
in WHO regions

6

Introduction

22

Policy Recommendations

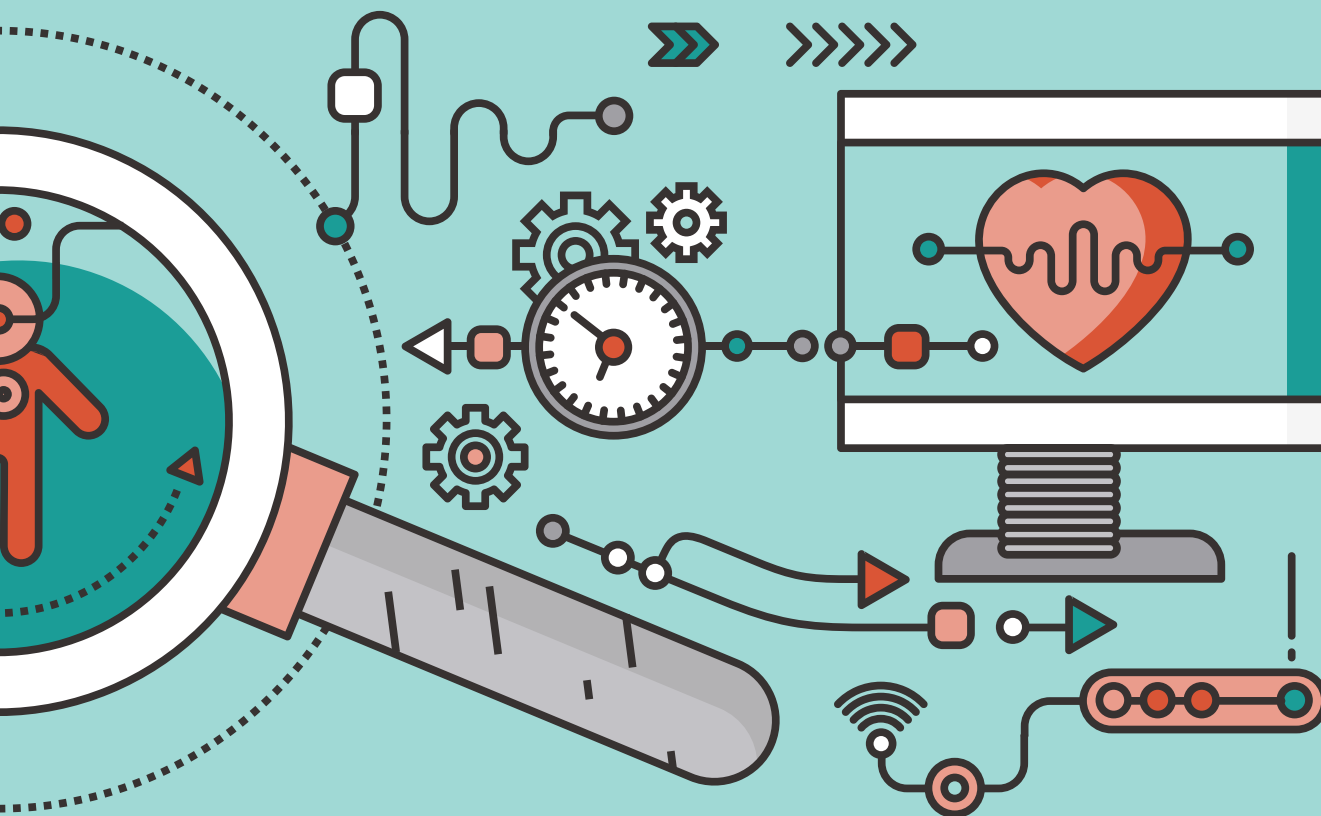
8

Pharmacovigilance for
Biotherapeutics

26

Case Studies





Foreword

Modern medicines have helped societies grow healthier and sustainably, changing the way in which diseases are addressed. For instance, improvements in existing cancer treatments have cut annual death rates by half in the United States. High cholesterol and other heart diseases, which required extensive treatment in the 1970s, can now be easily managed with oral therapy.

From drug discovery through approval, developing a new medicine on average takes at least 10 years. However, it is impossible to completely understand the safety profile of a medicine prior to its use: adverse drug reactions in patients (ADRs) – side effects – can occur at any time for several reasons. Therefore, all biopharmaceutical companies, countries and national regulatory authorities should have appropriate controls and measures in place to perform this important discipline.

The system that puts together all processes for monitoring and evaluating ADRs is called pharmacovigilance. Adequate pharmacovigilance boosts health and increases patients' trust in the health system. As patients are increasingly relying

on the use of modern, complex, biotherapeutic medicines for the treatment of diseases such as cancer, diabetes and arthritis, pharmacovigilance is even more critical to the detection of potentially rare side effects.

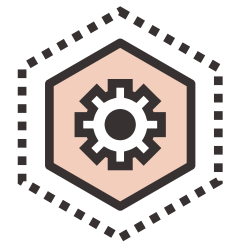
We all own pharmacovigilance: manufacturers, regulators, healthcare professionals, and patients. However, the complexity of it makes it often difficult to understand its importance and its applicability in everyday reality. That is why we asked Charles River Associates to investigate and identify some of the best practices and strategies, as well as the challenges, facing the pharmacovigilance of biotherapeutic and biosimilar medicines today.

This report aims to empower the broader health community in the science of pharmacovigilance, highlighting existing systems for improved reporting, data collection and monitoring and identifying several policy recommendations for the future.

01



Introduction



The International Federation of Pharmaceutical Manufacturers & Associations (IFPMA) asked Charles River Associates (CRA) to investigate “best practice” case studies on how different countries from every region in the world have implemented processes to address pharmacovigilance (PV) for biotherapeutic medicines. More specifically, the project had three objectives:

- *Improve understanding of the different approaches adopted globally in the six World Health Organization regions;*
- *Identify the extent to which these case studies address some of the challenges arising from biotherapeutic medicines; and*
- *Illustrate best practices by drawing on examples developed by national regulatory authorities and other stakeholders that could provide policy opportunities.*

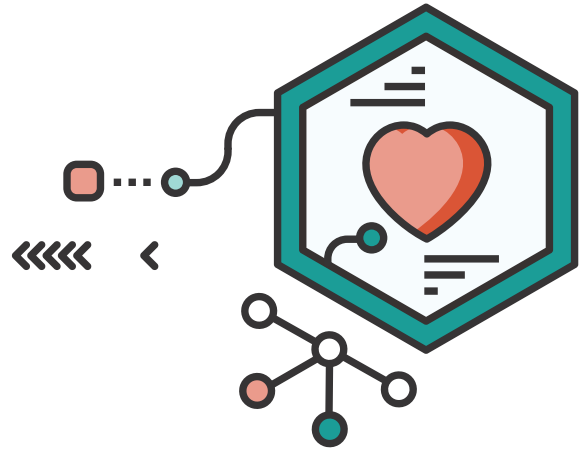
To develop the evidence base for this report, we selected examples from each of the WHO regions that were perceived as particularly “novel” or represented best practices in terms of addressing the challenges of biotherapeutic medicines. Examples from the following six countries or regions were selected:

Egypt, Indonesia, Japan, Mexico, The Southern African Development Community (SADC), and Turkey. In each of these countries, we carried out interviews with PV experts from pharmaceutical companies or representatives from regulatory authorities in the 6 countries or regions.

REGION	COUNTRY	ORGANIZATION
Eastern Mediterranean	Egypt	Egyptian Pharmaceutical Vigilance Center (EPVC)
South East Asia	Indonesia	Pfizer Indonesia
Western Pacific	Japan	Japan Pharmaceutical Manufacturers Association (JPMA)
Americas	Mexico/Brazil	Asociación Mexicana de Industrias de Investigación (AMIIF)
Africa	Southern Africa	Southern African Development Community (SADC)
Europe	Turkey	Araştırmacı İlaç Firmaları Derneği (AIFD)

02

.....

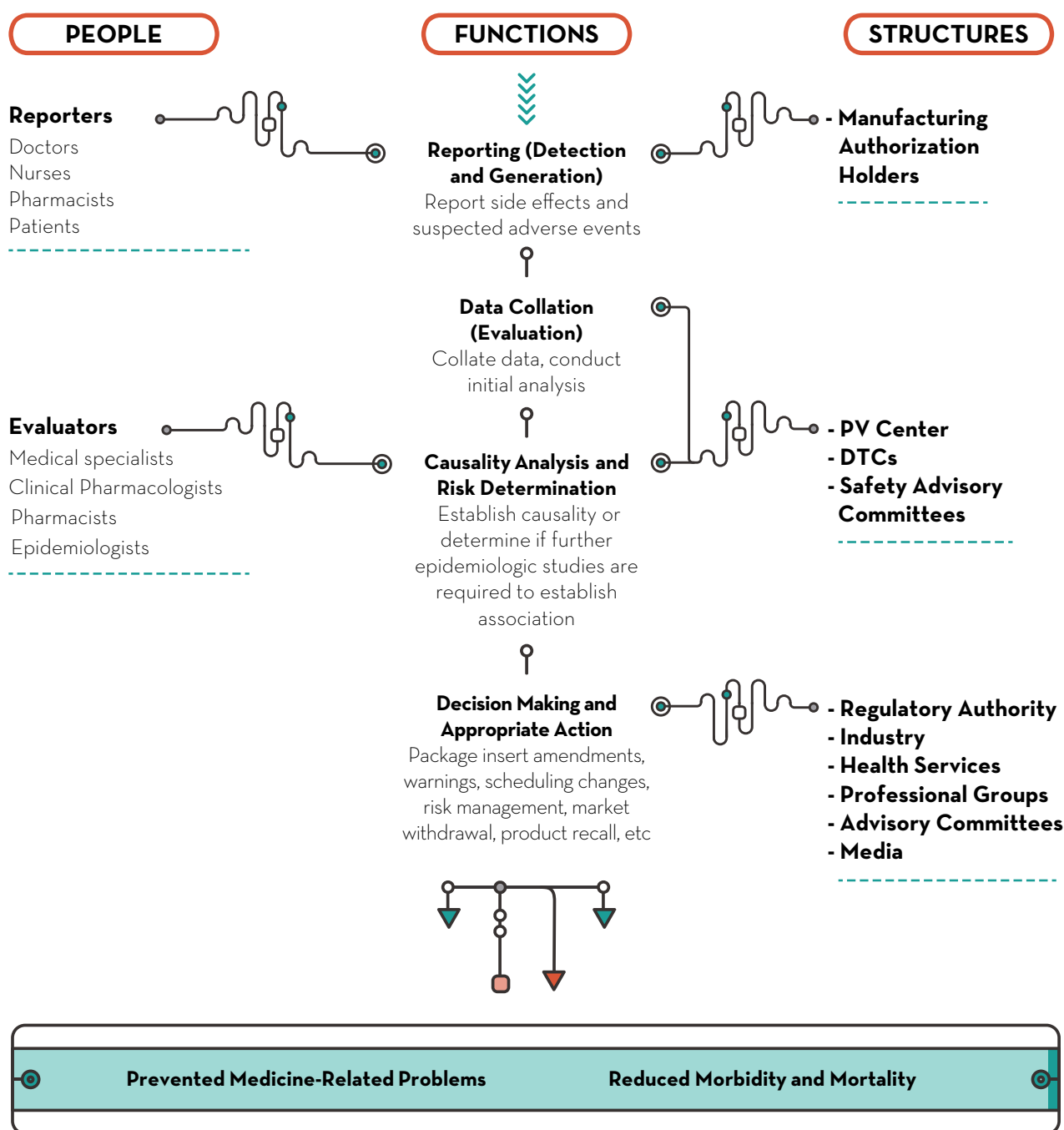


Pharmacovigilance for Biotherapeutics

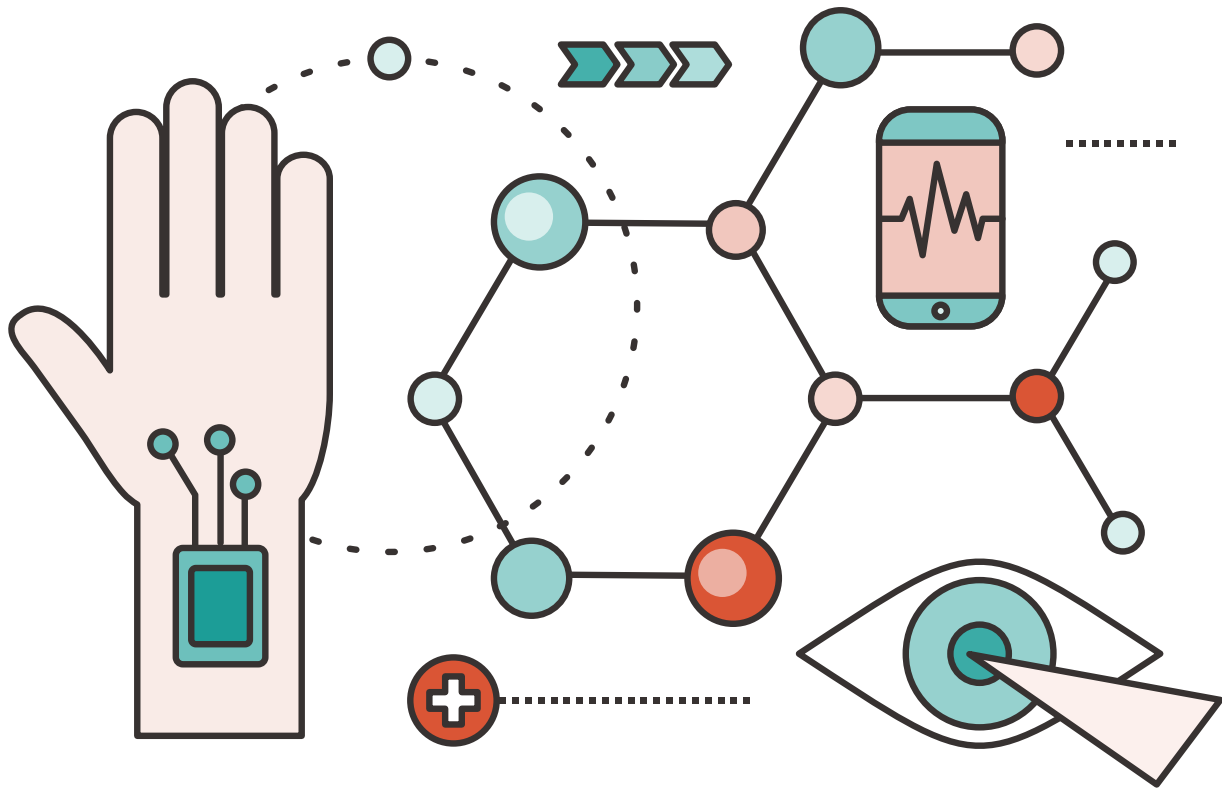


The aim of PV is to enhance patient care and patient safety in relation to the use of medicines; and to support public health programs by providing reliable, balanced information for the effective assessment of the risk-benefit profile of medicines.¹ Best practice for PV for traditional small molecule medicines is well known and has a number of attributes as illustrated in Figure 1. PV consists of identifying, reporting, and analyzing adverse drug reactions (“ADRs”) to create the data necessary for regulatory action. There are four main steps in the PV process: reporting, data collation, causality analysis and risk determination, and decision making and appropriate action.²

FIGURE 1. Components of a comprehensive, ongoing pharmacovigilance system.
Source: Adapted from Strengthening Pharmaceutical Systems (SPS). 2009.³



¹ WHO. Essential medicines and health products: Pharmacovigilance. Retrieved at http://www.who.int/medicines/areas/quality_safety/safety_efficacy/pharmvigi/en/
² Strengthening Pharmaceutical Systems (SPS) Program (2009). Indicator-Based Pharmacovigilance Assessment Tool: Manual for Conducting Assessments in Developing Countries. Submitted to the U.S. Agency for International Development by the SPS Program. Arlington, VA: Management Sciences for Health.
³ Strengthening Pharmaceutical Systems (SPS) Program. 2009. Indicator-Based Pharmacovigilance Assessment Tool: Manual for Conducting Assessments in Developing Countries. Submitted to the U.S. Agency for International Development by the SPS Program. Arlington, VA: Management Sciences for Health.



While the initial goals of PV focused almost entirely on detecting ADRs, the scope of PV has expanded and needs to address additional challenges, such as the need to monitor possible counterfeit medicines, adherence to good manufacturing practices, and training of healthcare professionals (HCPs) to recognize and report ADRs.⁴ This means that PV requires coordinated multi-level efforts to successfully minimize harm to patients, involving patients, policy makers, prescribers, manufacturers, regulatory authorities, and all HCPs.⁵

KEY CHARACTERISTICS OF BIOTHERAPEUTIC MEDICINES AND CHALLENGES ASSOCIATED WITH PV

Biotherapeutic medicines or biotherapeutics are used for the treatment, prevention or cure of disease in humans. They differ from chemically-synthesized small molecular weight drugs which have a well-defined structure and can be thoroughly characterized. Biotherapeutics are generally derived from living material (i.e. human, animal, or microorganism) are complex in structure, and thus are usually not fully characterized.⁶ It is well known that biotherapeutics are produced in a different manner to their small molecule counterparts and as such, they have different properties.

A MORE COMPLEX PRODUCTION PROCESS WITH INHERENT VARIABILITY

Biotherapeutics have a more complex production process with inherent variability between molecules and between individual batches of a given product. The significantly larger and more complex molecular composition of biotherapeutics combined with their heterogeneity due to the manufacturing process, means that manufacturers must collect additional evidence on the manufacturing process. In addition, post marketing data capture (i.e. information on the identity of the specific product and batch involved) can be challenging. Such product-specific safety surveillance is generally considered to be more relevant for complex medicines such as biotherapeutics than it is for small molecules.

THE POTENTIAL FOR GENERATING UNWANTED OR DELAYED IMMUNE RESPONSES

There is also a variety of different properties of biotherapeutics that lead to different reactions and eventually to adverse events. Small (undetected) differences compared with originator products might lead to unexpected immunogenicity in patients leading to unwanted immune reactions. Overall, it is also more challenging to understand the origin of

⁴ WHO (2002). The Importance of Pharmacovigilance: Safety Monitoring of medicinal products. Retrieved at <http://apps.who.int/medicinedocs/en/d/Js4893e/>

⁵ Ibid.

⁶ US FDA, Frequently Asked Questions About Therapeutic Biological Products Accessible at: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/20HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/ucm113522.htm>

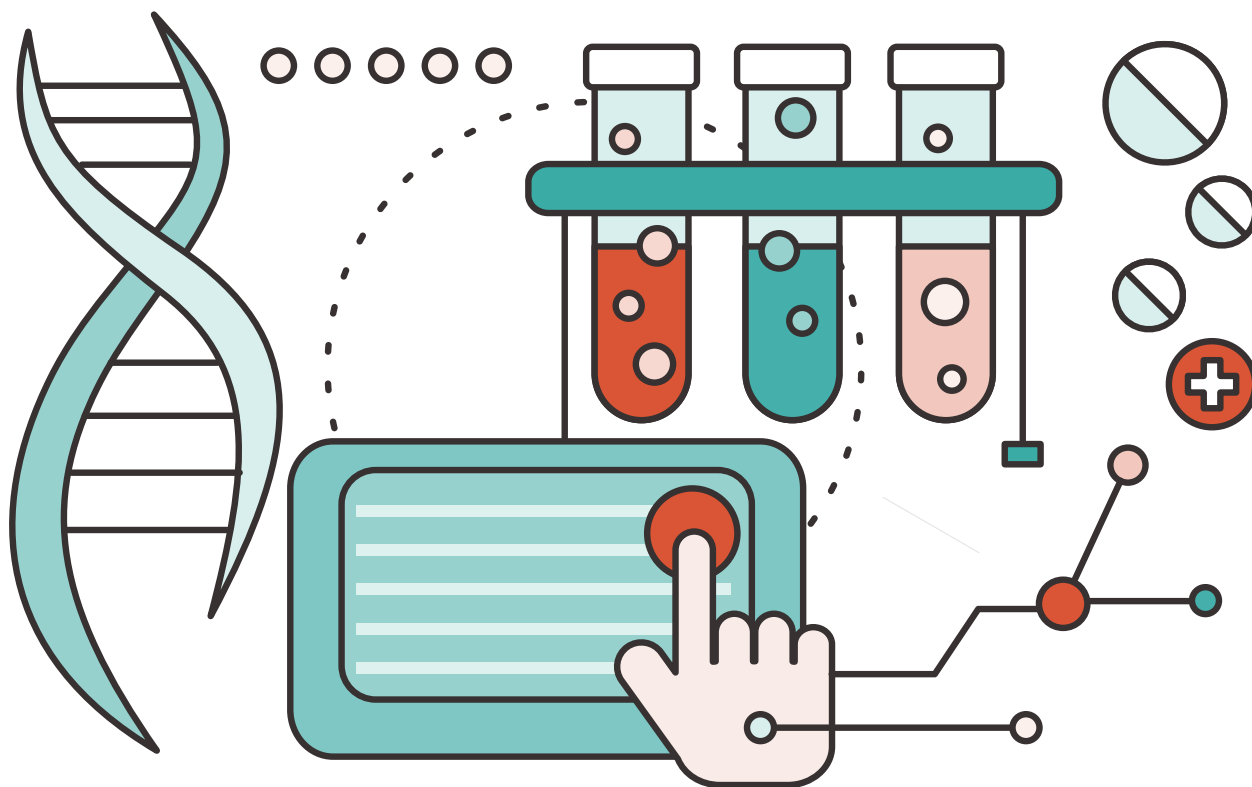
adverse reactions (or reduction in efficacy) as this can have multiple causes. This poses significant challenges to PV systems trying to uncover the underlying cause of an ADR.

SUPPLY CHAIN CHALLENGES


Biotherapeutics are also less stable than small molecules and sensitive to external conditions which can result in changes in expiry of the product.⁷ Even small storage changes can lead to physical modifications (and thus could potentially modify efficacy/safety). Biotherapeutics therefore require additional considerations regarding supply logistics and the monitoring of storage conditions and interpretation of the product's expiry.

In summary, given the aforementioned differences compared to small molecules, biotherapeutics raise a number of different challenges with respect to effective PV, these include:

1. Small changes in the production and purification process might alter the safety profile of the product;
2. More information needs to be gathered on the identity of the product involved;
3. Data capture for biotherapeutic medicines is more challenging;
4. It is more challenging to understand whether an adverse reaction or reduction in efficacy is due to the progression of the disease, immunogenicity/anti-drug antibodies (ADAs), or changes in products;
5. Biotherapeutic medicines require additional monitoring on storage conditions and on expiry date; and
6. Biosimilars are not exact copies of the original biotherapeutic medicine and any uncontrolled switching from the originator to the biosimilar needs to be appropriately taken into account.



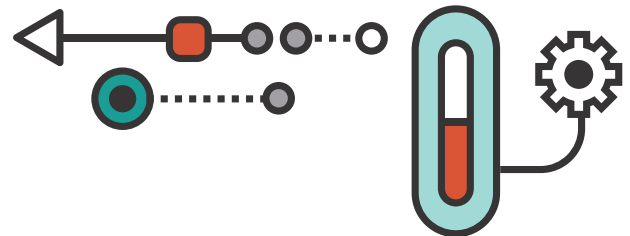
⁷ Van Hartingsveldt, B. (2013) Small Molecules vs Biologics Different Early Development? The Belgian Pharmaceutical Conference.



The significantly larger and more complex molecular composition of biotherapeutics combined with their heterogeneity due to the manufacturing process, means that manufacturers must collect additional evidence on the manufacturing process



03



Biotherapeutic Medicine Pharmacovigilance Strategies in WHO Regions

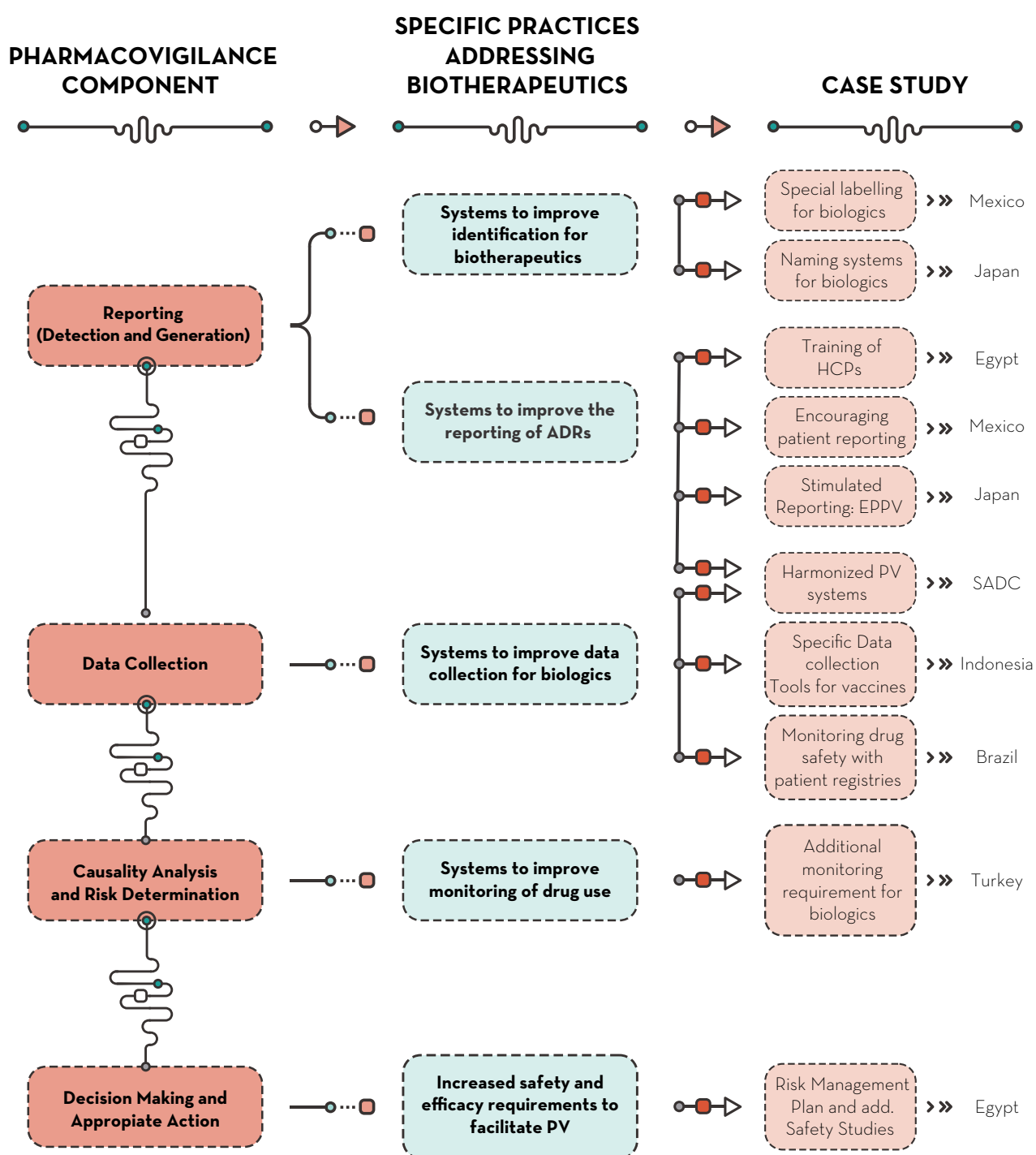


Within each PV function, there are certain strategies that regulatory agencies use to address the challenges raised by biotherapeutic medicines. We identified case studies that illustrate how the challenge of biotherapeutics can be addressed.

Figure 2 illustrates the selected case studies within this framework.

FIGURE 2. Pharmacovigilance for biotherapeutics - selected case studies.

Source: CRA analysis



SYSTEMS TO IMPROVE IDENTIFICATION FOR BIOTHERAPEUTIC MEDICINES

The first aspect of PV that has been tailored to address the particular challenges of biotherapeutics is the system that regulatory authorities use to identify, name, and label products.

NAMING SYSTEMS TO DISTINGUISH BIOTHERAPEUTICS

Establishing different names for biotherapeutic medicines is seen as crucial to PV. Adverse events can be linked directly to one product and its specific production process, expediting signal detection and response.

There has been considerable debate on naming conventions in many parts of the world. For example, in Europe, in the case of a suspected ADR relating to a biotherapeutic medicinal product, this product should be identified by its brand name as well as its INN (International Nonproprietary Name) and batch number. Meanwhile, Japan has implemented a unique naming system that distinguishes between biosimilars and their reference products, and several nations and regions have labelling requirements that help physicians identify the product's batch number and facilitates batch reporting to relevant authorities as part of the ADR reporting system.⁸ As described in *Case Study 1*, in Japan, both originator biotherapeutics and biosimilars start with the same INN, but biosimilars are followed with “biosimilar 1/2/3/etc.” depending on the order of approval.⁹ For marketing purposes, biotherapeutics and biosimilars can also use branded names that contain the manufacturer, formulation, and dosage strength. In such situations brand names must contain the initials “BS.” This is aimed at drawing the attention on the fact that biotherapeutics are not identical thereby lessening confusion and ensuring patient safety.

This naming system and ones similar to it are already in the process of being implemented in other countries. The WHO has recently finalized a scheme using Biological Qualifier codes which would be used in conjunction with the nonproprietary name of a biosimilar, in order to distinguish it from the reference

product and from other biosimilars. Individual countries should consider the best way to maintain high levels of access to more affordable biosimilars while still ensuring patient safety through distinguishable names.

SPECIFIC LABELLING FOR BIOTHERAPEUTIC MEDICINES

Given that small changes in the production and purification process of biotherapeutic medicines might alter the safety profile, even within the same product and manufacturer, it is important to differentiate between batches and clearly mark this information on product packaging. This is specifically important in many Latin American countries that may have non-comparable biotherapeutic products (“NCBPs”) on the market.¹⁰ Essentially, NCBPs often do not have robust data showing quality, safety, and efficacy on their own nor do they have data demonstrating their bioequivalence to an originator product.¹¹ The fact that many NCBPs can be used in the market without proper safety, efficacy, and quality data means that PV in this area must be more stringent and comprehensive to fully detect any and all issues that could arise with these products. In countries with NCBPs, PV systems must focus on gathering more post-marketing data from multiple sources, using appropriate naming systems that distinguish between reference products and NCBPs, and setting labelling standards that differentiate products.¹² As a result, some of these countries such as in Mexico have adopted specific labelling requirements for biotherapeutic products to be in place on the secondary packaging (see *Case Study 2*). These include additional requirements for biotherapeutic products whereby manufacturers must indicate the name and address of the manufacturer of active biological ingredient information, the initials “MB” on their label for innovator biotherapeutics or “MBB” for biosimilars, as well as a safety warning for products prepared from human blood or plasma or a specific batch number for specifications of life organism.¹³ Similarly to the nonproprietary naming system in Japan, this distinction helps HCPs distinguish between innovators and follow-ons in the case of adverse reactions.

⁸ See, for example: FDA (2014). Draft Guidance for Industry: Postmarketing Safety Reporting for Human Drug and Biological Products.; Egyptian Ministry of Health (2012). Draft Guideline for Registration of Biosimilar Products.; Iran FDO (2014). Biologics. Retrieved at <http://fdo.behdasht.gov.ir/index.aspx?siteid=114&pageid=40850>

⁹ Arato, Teruyo (2011). Recent Regulations of Biosimilars in Japan. Retrieved at <https://www.pmda.go.jp/files/000163979.pdf>

¹⁰ NCBP are intended to copy another biotherapeutic product but have not been directly compared or analyzed against an already licensed reference biotherapeutic product. These products have also not been approved via a regulatory pathway that is in alignment with the WHO similar biotherapeutic product guidelines that ensure quality, safety, and efficacy. A NCBP is not a biosimilar because NCBPs have not been shown to be similar to the reference product in these three core areas.

¹¹ IFPMA (2014). NCBPs Policy Statement.

¹² Ibid.

¹³ Ministry of Health (2012). Mexican Official Standard NOM-072-SSA1-2012, sections 5 and 6.

SYSTEMS TO IMPROVE THE REPORTING OF ADRs

Another important challenge for biotherapeutics medicines is to understand whether the adverse reaction or reduction in efficacy is due to the progression of the disease, immunogenicity/ADAs, or changes in products (due to storage/expiry/quality) and additional monitoring on storage conditions and expiry for biotherapeutics is required. Initiatives to improve PV systems for biotherapeutics are only useful if the quality and quantity of ADR reports are adequate.

TRAINING OF HCPS TO ENCOURAGE REPORTING

Sophisticated reporting systems are still subject to the limitations that any passive surveillance system faces. Primary among these is underreporting, differential reporting and other reporting biases. Cognizant of this issue, several countries have launched training or awareness programs to help raise the level of reporting. One example of this can be found in Egypt where the Ministry of Health has taken strong measures to address the issue of underreporting of ADRs. In 2011, the Egyptian Pharmaceutical Vigilance Center (EPVC) organized several training activities in cooperation with local trade associations, professional associations, and academics to increase the capacity and awareness of medical professionals in understanding PV and risk management assessment, according to a PV expert in Egypt (see *Case Study 3*).¹⁴ Training programs such as the one in Egypt do not require very extensive resources; with only a few trained individuals needing to travel around the country to administer the programs. Studies in other countries such as Sudan¹⁵ and Nepal¹⁶ have indicated that training could be successfully implemented to help improve reporting rates. HCP training programs are particularly applicable to many emerging markets where other best practice strategies may be impractical or difficult to implement.

ENCOURAGING REPORTING THROUGH PATIENT GROUPS

In other countries, such as Mexico, non-governmental groups have worked to encourage direct patient reporting of ADRs. As described in *Case Study 4*, the Ale Association, a non-profit organization that supports and promotes organ donation in Mexico

Reporting by patient groups has the potential to increase knowledge about the possible harm of medicines and has been incorporated into PV systems in several countries

through different outlets, has launched a program to organize and mobilize patients to generate data to show regulators the importance of a more unified ADR reporting system.¹⁷ It has been shown that reporting by patient groups has the potential to increase knowledge about the possible harm of medicines and has been incorporated into PV systems in several countries. However, the fact that patients are not trained in reporting ADRs could represent a serious problem if patient reports are accepted without review. The role of patient reporting in PV systems should be incorporated into the PV system with care to maximize these benefits while avoiding potential pitfalls.

STIMULATED REPORTING: EARLY POST-MARKETING PHASE VIGILANCE SURVEILLANCE

Several initiatives have been used to encourage and facilitate HCP reporting in specific situations (e.g., hospital settings) for new products or certain time periods. Manufacturers can help stimulate the ADR reporting in the early post-marketing phase as part of their regular visits to HCPs by providing safety information to the general population early in use (e.g., Early Post-marketing Phase Vigilance, EPPV in Japan). Since this is a form of spontaneous event reporting; data obtained from stimulated reporting cannot be used to generate accurate incidence rates but reporting rates can be estimated.¹⁸ This is the case in Japan (see *Case Study 5*) who has encouraged stimulated reporting by leveraging pharmaceutical sales representatives. In 2000, Japan introduced a system that requires pharmaceutical companies to draw the attention of medical professionals to report accurate information and promote understanding of

¹⁴ Interview with EPVC (2015).

¹⁵ Elnour, AA et al. (2009). Awareness and reporting of adverse drug reactions among health care professionals in Sudan. *Journal of Quality Patient Safety*, 35(6).

¹⁶ Santosh, KC et al. (2013). Attitudes among HCPs to the reporting of ADRs in Nepal. *BMC Pharmacology and Toxicology*, 14(16).

¹⁷ Asociación ALE (2015). What we do. Retrieved at <http://asociacionale.org/en/>

¹⁸ US FDA (2005). Guidance for Industry E2E Pharmacovigilance Planning - April 2005 ICH.

Retrieved from: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073107.pdf>

proper use over a period of 6 months from the launch of new products, and for Ministry of Health, Labour & Welfare (MHLW) to rapidly collect information on serious ADRs and infections by requesting companies to cooperate in collection of ADR information and to take the necessary safety measures, thus minimizing the effects of damage caused by ADRs.¹⁹

Active reporting mechanisms such as the Early Post-marketing Phase Vigilance in Japan are an effective way to encourage reporting in countries where the monitoring and reporting culture amongst HCPs is low. In most countries, company medical representatives are present and involved in communicating information to HCPs on the appropriate use of the drug anyway, so no additional infrastructure is necessary, making this an easy and effective measure to put in place in almost all countries with a pharmaceutical industry.

SYSTEMS TO IMPROVE DATA COLLECTION FOR ADRs

Another set of strategies used to respond to the challenges of bioterapeutics is ensuring that the infrastructure necessary for reporting is extensive and intuitive. Databases and tracking systems like those in the US can help collect and follow ADRs over a large population. Clinical registries (collecting patient data) have also become more widely used for collecting post-marketing surveillance data as they offer a more representative picture of the range of patients receiving a drug, their additional medications, and existing medical conditions than is contained in other clinical investigations.²⁰

INFORMATION TECHNOLOGY (IT) SYSTEMS AND REPORTING DATABASES FOR VACCINES REPORTING

One way to help to improve data collection includes developing IT systems and reporting databases. One area where this is particularly relevant is for vaccines (a subset of bioterapeutics), which are seen as particularly challenging in pharmacovigilance due to their complexity; specifically adverse events following immunization (“AEFIs”) can be directly symptomatic of the attenuated virus or related to a completely different component of the vaccine antigen. Each part of the vaccine has unique

Databases and tracking systems like those in the US can help collect and follow ADRs over a large population

safety implications, requiring greater attention and monitoring than other drugs.

In order to better identify vaccine safety concerns, countries have sought to “widen the net” of reporting so that even rare events can be more easily connected. Amalgamated vaccine reporting systems, by streamlining and simplifying the reporting process across larger areas, simultaneously encourage more reporting from patients or HCPs while expanding the usual range of data collection. We highlight the case of the US who has developed a national vaccine safety surveillance program called Vaccine Adverse Event Reporting System (“VAERS”) that collects information concerning AEFIs from patients, public health providers, parents, HCPs, and caregivers. In many emerging markets, the ADR reporting process is often slow as reports are communicated by post or email, causing large build-ups, queues, and lags.

Other countries, such as Indonesia, have also implemented a database system to record AEFIs called the Vaccine Reporting System (VRS). Under the new VRS introduced by Indonesia’s PV Unit, the requirements for vaccines are quite stringent relative to other products in terms of deadlines for reporting (see *Case Study 6*). Vaccines require much faster reporting and a specific format. While the reporting time limit for ADRs is 15 days, initial AEFI reports should be sent to VRS within 24 hours and companies must also send a follow-up report within 15 days.²¹ Today, Indonesia still faces challenges in ensuring HCPs use the system and the PV Unit perceives reporting rates as low.²² To complete the value of the VRS system, the government has also introduced a special campaign dedicated to educating HCPs about how to report using the system.

¹⁹ JPMA (2001). One Year after “Early Post-marketing Phase Vigilance Surveillance”. Japan: Japan Pharmaceutical Manufacturers Association.

²⁰ Willis, C. D., McNeil, J. J., Cameron, P. A., & Phillips, L. E. (2012). Monitoring drug safety with registries: useful components of postmarketing pharmacovigilance systems. *Journal of clinical epidemiology*, 65(2), 121-125.

²¹ Ibid.

²² Ibid.



It should be recognized that developing a national database and providing national training for HCPs, industry, and hospitals is not inexpensive. However, support for such activities was provided by the WHO.

MONITORING DRUG SAFETY WITH PATIENT REGISTRIES

Biotherapeutics are more commonly involved in specialized treatment and are also commonly involved in the treatment of concomitant diseases. It is therefore often difficult to fully appreciate the underlying cause of the relevant ADR. The development of a registry of patients in a particular clinical setting provides reliable estimates of the incidence of adverse events across defined populations.²³ Interest in registries as post-marketing surveillance tools for specialized pharmaceuticals continues to gain attention from manufacturers, academics, regulatory authorities, and subsidising schemes, such as the Bosentan Patient Registry (BPR) introduced by the Pharmaceutical Benefits Scheme (PBS) in Australia.

Other countries such as Brazil or India have also started to introduce patient registries as a post-marketing surveillance tool. One example is the BIOBADASER / BIOBADAMERICA registry in Brazil (see *Case Study 7*) which actively collects information on relevant

adverse events occurring with long-term treatment with biotherapeutics. Patients enter the registry when they receive the first biotherapeutic medicine and are followed-up with indefinitely, even after having discontinued the treatment.

In 2006, BIOBADASER, a registry hosted by the Spanish Society of Rheumatology (SER) was re-designed into BIOBADASER 2.0, which included a new web-based platform that improved navigation speeds and data collection. Additionally, the new platform allowed for continuous online monitoring and facilitated the interaction between ADR monitors and collection centers.²⁴ BIOBADASER has spread as a template for other registries in other countries as well. In 2007, several Latin America countries signed party agreements to replicate the register locally, called BIOBADAMERICA. Each national register, such as the one in Brazil, has its own governance and staff; SER members train staff through an online course in how to collect, monitor, and analyse the register data.²⁵

Widespread data collection is also useful for epidemiological research—BIOBADAMERICA and other registries have been used to compare the risks of adverse effects of medicines across countries and continents.²⁶

²³ Willis, C. D., McNeil, J. J., Cameron, P. A., & Phillips, L. E. (2012). Monitoring drug safety with registries: useful components of postmarketing pharmacovigilance systems. *Journal of clinical epidemiology*, 65(2), 121-125.

²⁴ Carmona, L. et al. (2014). BIOBADASER, BIOBADAMERICA, and BIOBADADERM: safety registers sharing commonalities across diseases and countries. *Clinical and Experimental Rheumatology*, 32 (85).

²⁵ Ibid.

²⁶ Maini et al. (2014). The global challenges and opportunities in the practice of rheumatology: White paper by the World Forum on Rheumatic and Musculoskeletal Diseases. *Journal of the International League of Associations for Rheumatology*.

MINIMUM STANDARDS FOR PV THROUGH HARMONIZATION

Given the challenges associated with biotherapeutic medicines, e.g. more difficult data capture, the introduction of minimum standards can be very beneficial. Indeed, it is important that information on the identity of the biotherapeutic medicine involved is effectively gathered. Harmonization of standards across a whole region could enable information to be gathered more effectively for the more complex use of biotherapeutics. One example of this can be observed through the efforts of the Southern African Development Community (SADC)²⁷, established in 2002, as part of the Pharmaceutical Programme under the SADC Secretariat's Directorate of Social and Human Development and Special Programmes (see *Case Study 8*). The SADC is undertaking a campaign to 'harmonize' the PV systems across all SADC countries by introducing a 'minimum standard' designed to improve the quality, safety and efficacy of medicines circulating within the region, and to establish and maintain a regional shared network system for regulatory authorities.²⁸ A key component of the harmonization process involves setting up a center that can collaborate with other centers (within or outside the country) and health authorities to be able to report, capture and provide data to process ADRs but also to ensure that information is uniform (in terms of WHO standards) and provide some development or components for training (e.g. on data collection, analysis, risk management).²⁹ Since the introduction of the harmonization, countries have progressed from one category to the next to harmonize the approaches to PV.³⁰

SYSTEMS TO IMPROVE THE MONITORING OF DRUG USE

One particular difficulty in monitoring biotherapeutic medicines is that they are commonly used by a small patient population. Not only does this mean that biotherapeutics medicines may have to rely on smaller sample sizes during the clinical stage, but it implies that the risk of ADRs for biotherapeutics will be even more difficult to assess since reports will likely be few and far between. PV for biotherapeutics therefore requires a certain level of granularity, sensitivity, and targeted monitoring for appropriate signal detection. To achieve this, some countries and regions have started to implement universal minimum requirements for PV.

ADDITIONAL MONITORING REQUIREMENT FOR BIOTHERAPEUTICS

Another way to improve the monitoring of drug use is to place biotherapeutics on "additional monitoring lists," which are essentially categories of medicines that have supplementary monitoring regulations. In Turkey, the Arab League, and the European Union (EU), additional monitoring requirements have been introduced to address the increased risk potentially associated with biotherapeutic medicines. One example of this can be found in Turkey (see *Case Study 9*). In April 2014, Turkey adopted the EU's additional monitoring list using the exact language from the EU regulation. As in the EU regulation, Turkey introduced an "additional monitoring list" to encourage more intensive observation of high-risk drugs. Whilst this is not specific to biotherapeutic medicines, it largely includes many biotherapeutics and all blood products. Medicines on this list are marked with a black inverted triangle displayed on the drug's packaging. The black triangle highlights the need for surveillance of any ADRs that might arise from the use of a new medication. While implementation of a 'black triangle' labelling system has been slow to gain traction, the fact that other nearby countries are also attempting to implement black triangle labelling has made the process easier for pharmaceutical companies operating in Turkey. Turkey has paired the additional monitoring list with active hospital observation programs and more stringent monitoring policies in some hospitals during a pilot project in Izmir and Ankara. This is a good example of a country going beyond standards established by existing stringent regulatory agencies to ensure that safety risks specific to their country are addressed.

INCREASED SAFETY AND EFFICACY REQUIREMENTS TO FACILITATE PV

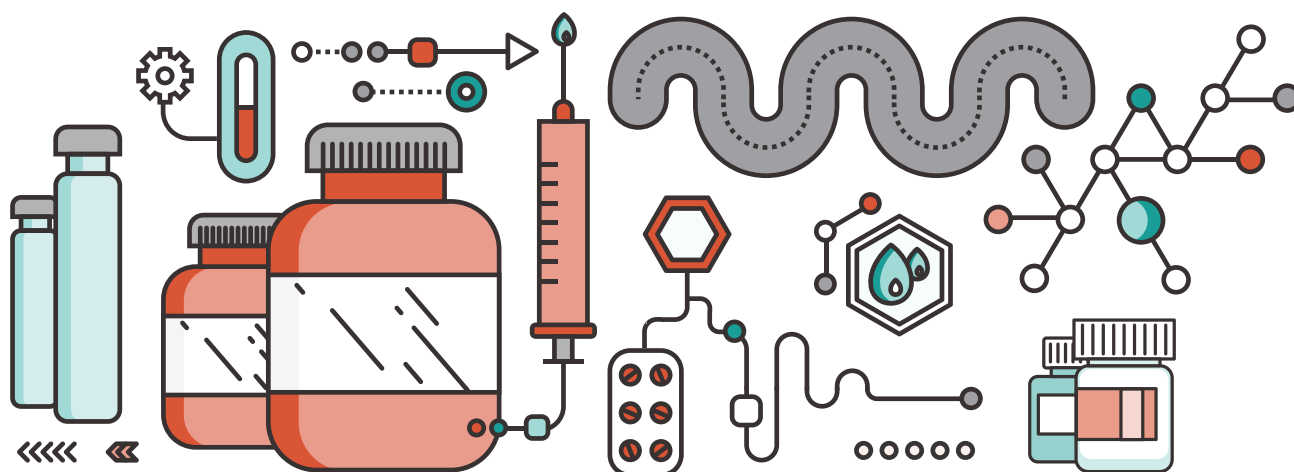
In general, biotherapeutics present unique manufacturing and lifecycle challenges. In response to this, regulatory authorities around the world have developed increased safety and efficacy requirements to facilitate PV for biotherapeutics and vaccines. Risk management plans (RMP)³¹ generally describe potential safety concerns associated with a drug and the steps companies plan to take post-approval to continuously ensure the safety of their products.

²⁷ There are 15 SADC countries, which display a vast difference in terms of levels of development. Some are upper middle income (e.g. Botswana, South Africa), others lower middle income (e.g. Angola, Zambia), and others low income (e.g. Malawi, Zimbabwe).

²⁸ ICH, Southern African Development Community (SADC), available at: <http://www.ich.org/about/organisation-of-ich/coopgroup/sadc.html>

²⁹ Interview with SADC (2015).

³⁰ Interview with SADC (2015).



Regulatory authorities like the European Medicines Agency (EMA) require RMPs submitted for bioterapeutics to include a description of the potential safety issues associated with the product, including those arising from the differences in manufacturing processes between the biosimilar and its reference product.³²

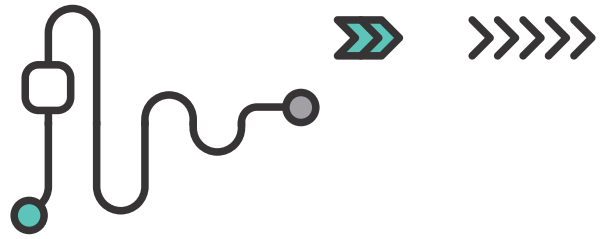
In Egypt, one important step taken by the Egyptian Pharmaceutical Vigilance Center (EPVC) in 2010 was to finalize the regulatory PV guidelines based mainly on the EU PV guideline drafted by the EMA and published by the European Commission (see *Case Study 10*). However, all PV requirements were tailored by the EPVC to address local needs and ensure all these local characteristics for PV were taken into account and reported on. This includes the introduction of a requirement that the local Egyptian affiliate of the company had to provide. Since July 2012, local Egyptian affiliates have been required to submit the following PV documents as part of the Registration dossiers, a detailed description of how the PV process applied in Egypt as well as a description of how PV relates to local infrastructure (e.g. Standard Operating Procedures (SOP) at local level). According to a local PV expert, the development of local PV guidelines had encouraged small local companies to upgrade their PV capabilities and multinational companies operating in Egypt to develop local capabilities.

Turkey has paired the additional monitoring list with active hospital observation programs and more stringent monitoring policies in some hospitals during a pilot project in Izmir and Ankara. This is a good example of a country going beyond standards established by existing stringent regulatory agencies to ensure that safety risks specific to their country are addressed

³¹ A RMP is a documented plan that describes the risks (adverse drug reactions and potential adverse reactions) associated with the use of a drug and how its risks will be prevented and or minimized in patients.

³² Zuniga, L. and B. Calvo, "Biosimilars: pharmacovigilance and risk management," *Pharmacoepidemiology and Drug Safety*, 19(7), July 2010, pp. 661-669.

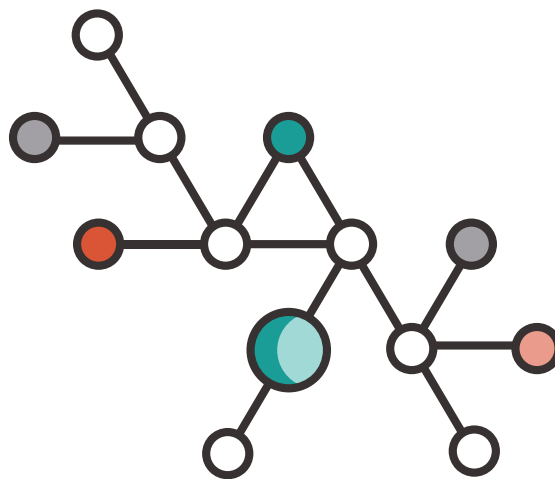
04



Policy Recommendations

.....





This report describes and assesses practices and systems in community and hospital settings for reporting and tracking biotherapeutic drug-related adverse events drawing from case studies selected across the 6 WHO regions. Although the countries in this report have all utilized different strategies to overcome the challenges raised by biotherapeutic medicines, there are some common points of successes and failures from which we can draw more general lessons. Drawing on these experiences, we suggest 5 policy recommendations to improve pharmacovigilance to address the challenges associated with biotherapeutic medicines:

SYSTEMS TO IMPROVE IDENTIFICATION FOR BIOTHERAPEUTIC MEDICINES SHOULD REFLECT THE CHALLENGES AND NEEDS RELEVANT TO EACH LOCATION

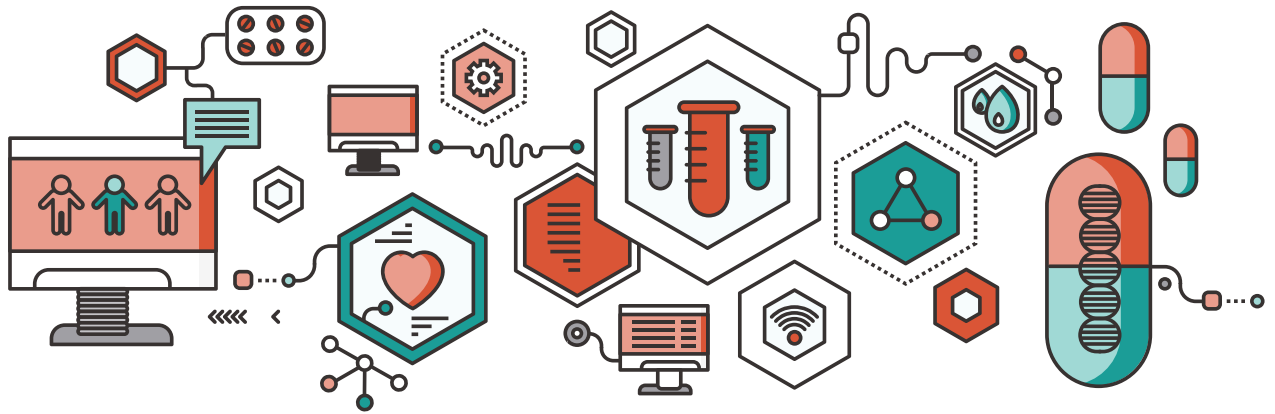
The need to improve the identification of medicines is well recognized and this is especially relevant for biotherapeutic medicines. There has been considerable debate on naming conventions for biotherapeutics in many parts of the world. Systems that regulatory authorities use to identify, name, and label products should reflect the challenges and needs relevant to

each country context. This can take different forms: products could be identified by its brand name as well as its INN and batch number; a unique naming system can distinguish between biosimilars and their reference product; labelling requirements that help physicians identify the product's batch number and facilitates batch reporting to relevant authorities as part of the ADR reporting system; as well as additional safety warnings for specific products. Other countries which encounter high levels of counterfeit drug activity may require more sophisticated identification mechanisms that attach unique codes to products that HCPs and patients can use to check their authenticity.

Training programs do not require significant resources and are particularly applicable to many emerging markets where other best practices strategies may be impractical or difficult to implement

DEVELOP INITIATIVES TO IMPROVE REPORTING RATES

Capturing adequate information (i.e. on the identity of the product involved) is important for biotherapeutics medicines due to their unique product characteristics, complexity and biological nature, yet can be more challenging than it is for small molecules. Any successful PV system must be built on a culture of both high ADR reporting rates and high quality reporting. Several experts noted that infrequent reporting was one of the main detriments of PV in their country, especially if their PV network was based on more passive measures. ADR reporting rates are particularly low in emerging markets, largely due to a lack of awareness and accessibility of reporting infrastructure and processes.



In this sense, initiatives to improve reporting rates by educating HCPs or patients are perhaps the most efficient ways to boost PV. Training programs do not require significant resources and are particularly applicable to many emerging markets where other best practices strategies may be impractical or difficult to implement.

Others have tried to maximize the benefits of existing reports by creating overarching reporting systems that aggregate reported data across larger regions. When aggregating data, PV systems can help ensure the accuracy of information by standardizing labelling and naming of medicines. By widening the net of data collection, these countries will be able to more accurately detect and target safety signals. This is particularly useful for bioterapeutics that are used in specific and small populations.

ENSURE THAT CASE REPORTS ARE OF SUFFICIENTLY HIGH QUALITY

Another important element of reporting, which is often ignored, is the importance of receiving case reports of sufficiently high quality. Reports that do not provide the necessary data are limited in their usefulness. This is illustrated in the case study of Early Post-marketing Phase Vigilance system that have been designed to actively collect more detailed information on each case directly from the activities of the medical representatives.

COMBINE PASSIVE PROGRAMS WITH ACTIVE APPROACHES

There are drawbacks to passive reporting that are extremely difficult to overcome; namely, these systems rely on HCPs setting aside time to submit ADRs,

which they often have little incentive to do. This is why risk management plans tend to pair passive programs with active approaches that locate safety signals. Active approaches are commonly used in the initial post-marketing phase for newly authorized medicinal products, including new bioterapeutics, and may also be included in the risk management plans for biosimilars. Active reporting mechanisms such as the Early Post-marketing Phase Vigilance are also an effective way to encourage reporting in countries where the monitoring and reporting culture amongst HCPs is low. This does not require additional infrastructure, making this an easy and effective measure to put in place in almost all countries with an active pharmaceutical industry.

TAILOR INTERNATIONAL GUIDELINES TO MEET SPECIFIC LOCAL CHALLENGES

Countries that tailor international guidelines to meet specific local challenges generally have more efficient PV systems and regulations. In this way, limited resources can be directed to the areas of most need. While harmonized regulations are useful to a certain extent in standardizing and streamlining PV processes, it is important for each country to consider the potential effects of each policy before implementing it locally. There is no single “right” PV system—it takes extensive knowledge of local epidemiology, culture, and health systems to craft the best network of policies in each country. The development of local PV guidelines has encouraged small local companies to upgrade their pharmacovigilance capabilities and multinational companies operating in Egypt, for example, to develop local capabilities. Companies are starting to pay more attention to local requirements and have brought the attention of their headquarters to them by hiring dedicated local staff for PV (e.g. Qualified Person Responsible for Pharmacovigilance, or QPPV).

Active reporting mechanisms such as the Early Post-marketing Phase Vigilance are also an effective way to encourage reporting in countries where the monitoring and reporting culture amongst HCPs is low



CASE STUDY 1

Specific naming systems for biotherapeutics

Establishing different names for biotherapeutic medicines is an effective way to improve identification of products and help distinguish biotherapeutics. Adverse events can be linked directly to one product and its specific production process, expediting signal detection and response.

JPMDA Non-Proprietary Names for biotherapeutic products

MOTIVATION

In the early 2000's, Japan was facing similar issues as the rest of the world regarding the distinction between biotherapeutic medicines.³³

APPLICATION

Japan's medicines regulatory agency JPMDA implemented a naming system for biotherapeutics and biosimilars in 2009 that takes these challenges into account. Their naming system is built on INNs, but includes additional signifiers

to help delineate between drugs. INNs are unique for each substance, but pharmacologically-related substances share a common "stem" so HCPs can easily recognize that the substance belongs to a group and has similar pharmacological properties.³⁴

SUCCESSES AND CHALLENGES

It is now easier to trace which product was administered to the patient in this sense. One interesting consequence

of this system is that it allows biosimilar companies to use the originator brand name provided they add "BS" and a number. However, if a physician writes a prescription for the original brand, the pharmacist cannot change the prescription to a generic.

TRANSFERABILITY

This naming system and ones similar to it are already in the process of being implemented in other countries; again, the WHO has recently proposed a very similar scheme using Biological Qualifier codes.

³³ Email from JPMDA (2015).

³⁴ WHO. Guidance on INN. Retrieved at <http://www.who.int/medicines/services/inn/innguidance/en/>

CASE STUDY 2

Specific labelling for biotherapeutic medicines

Small changes in the production and purification process of biotherapeutic medicines might alter the safety profile, even within the same product and manufacturer. It is therefore important to differentiate between batches and clearly mark this information on product packaging.

Specific labelling for biotherapeutic medicines in Mexico

MOTIVATION

In Mexico, physicians in the private sector tend to prescribe by brand name while those in the public sector or hospitals use the INN name; this is one of the reasons why it's important for labels to contain all of the above information.³⁵

APPLICATION

The medicines regulatory agency COFEPRIS has introduced additional labelling for biotherapeutics.³⁶

Mexican labelling requirements state that innovator biotherapeutics must have the initials "MB" on their label, while biosimilars should have "MBB."³⁷

SUCCESSSES AND CHALLENGES

The fact that biosimilars are all assigned the same code means that HCPs are obligated to take an additional step when they report an adverse drug reaction (ADR), since they have to track down the name of the manufacturer

and batch number of the product. As a Mexican PV expert noted, when using "the code with the generic name to report an adverse event, you need to include additional information."³⁸

TRANSFERABILITY

More specific labelling requirements for countries should reflect the challenges and needs relevant to each location (e.g. countries with very hot or humid climates, this may take the form of additional instructions on how to store medicine packages).

³⁵ Interview with Asociación Mexicana de Industrias de Investigación Farmacéutica (AMIIF) (2015).

³⁶ Federal Commission for the Protection against Sanitary Risk.

³⁷ Ministry of Health (2012), Mexican Official Standard NOM-072-SSA1-2012, sections 5 and 6.

³⁸ Interview with AMIIF (2015).



CASE STUDY 3

Training HCPs to encourage reporting

Another important challenge for biotherapeutics is to understand whether the ADRs are due to the progression of the disease, immunogenicity/ADAs, or changes in product conditions. Additional monitoring of the biotherapeutic product is required and greater level of reporting of ADRs bring significant benefits to PV.

Training of HCPs to encourage reporting in Egypt

MOTIVATION

Less than 3% of ADR reports come from the developing world, even though these countries make up 80% of the global population. Similar to other emerging markets, the Egyptian PV system is strongly affected by underreporting of ADRs.

APPLICATION

The Egyptian Pharmaceutical Vigilance Center (EPVC) decided to tackle the latter of these issues by integrating HCP training into the Egyptian PV system to enhance reporting of

ADRs, including reports of adverse events from biotherapeutics. In 2011, the Clinical Pharmacology Unit in Egypt developed a mechanism for ADR-reporting involving different departments at Ain Shams University Hospitals (ASUH).³⁹

SUCCESSSES AND CHALLENGES

Since the EPVC initiated their training programs, the rate of ADR reporting has increased to a small degree. After participating in the workshops, 96.3% of HCPs were willing to participate in Egypt's national ADR

reporting mechanism, and 92.2% of medical and 75% of pharmacy students learned how to correctly fill out an ADR report. Clearly, the HCP training program in Egypt is effective, but it must be expanded to include other regions and hospitals in the country.⁴⁰

TRANSFERABILITY

Training programs such as the one in Egypt do not require expensive resources; cases can simply be adopted off of ones that commonly occur at local hospitals, and only a few trained individuals need to travel around the country to administer the programs.

³⁹ Interview with EPVC (2015).

⁴⁰ Aboul-Fotouh, S. et al. (2011). Implementing an Egyptian PV system: University and Public Hospitals' Experience. Third International Conference for Improving Use of Medicines.



CASE STUDY 4

Encouraging reporting through patient groups

In some countries, non-governmental groups in countries have worked to encourage direct patient reporting of ADRs.

Patient focused reporting initiatives in Mexico

MOTIVATION

The combination of the lack of reporting culture amongst HCPs and the lack of active reporting means that patients groups have decided to become more involved in monitoring and reporting of ADRs.

APPLICATION

Some patient advocacy groups in Mexico have launched programs to organize and mobilize patient groups in demanding better quality healthcare. A part of this initiative, the Ale

Association, a non-profit organization that supports and promotes organ donation in Mexico through different outlets, is to educate doctors and patients in reporting adverse medical events.⁴¹ The Ale Association hopes to obtain official approval of their reporting site from COFEPRIS and then use the tool to present reports of their results to regulatory authorities.⁴²

SUCCESSES AND CHALLENGES

There is no quantitative data available on the success of this initiative,

but studies have shown that patient reports generally have higher quality and more detailed information than reports submitted by HCPs, most likely because HCPs file reports under greater time constraints.

TRANSFERABILITY

Patient advocacy associations exist around the world, although they are often more developed in the US, EU, and other high-income countries. However, not every patient advocacy group has a branch focused on increasing ADR reporting.

⁴¹ Asociación ALE (2015). What we do. Retrieved at <http://asociacionale.org/en/>

⁴² International Alliance of Patients' Organisations (2014). Challenges in achieving quality in healthcare. Retrieved at <https://www.iapo.org.uk/sites/default/files/files/Q1%20Challenges%20in%20achieving%20quality%20in%20healthcare.pdf>



CASE STUDY 5

Stimulated Reporting

Manufacturers can help stimulate the ADR reporting in the early post-marketing phase as part of their regular visits to HCPs by spontaneously providing safety information to the general population early in use.

Early Post-marketing Phase Vigilance in Japan

MOTIVATION

In Japan, there is no defined timeframe for reporting by HCPs.⁴³ However, it is acknowledged that close communication with medical specialists is essential to rapidly collect information on serious ADRs.

APPLICATION

Japan introduced new “active” mechanisms of passing along information efficiently and exhaustively to HCPs about the appropriate use medicines needed to be developed. The concept of “Early Post-marketing Phase Vigilance (EPPV)”

was introduced in October 2001 requiring pharmaceutical companies to draw attention of medical professionals to report accurate information and promote understanding of proper use over a period of 6 months from the launch of new products.⁴⁴

SUCCESSSES AND CHALLENGES

Whilst the number of safety reports submitted to the authorities has greatly increased since 2009, it has been argued that this is largely due

to increasing foreign cases reported. However the EPPV policy has helped obtaining enough information for the evaluation of most Japanese cases.

TRANSFERABILITY

In most countries, company medical representatives are present and involved in communicating information to HCP on the appropriate use of the drug so no additional infrastructure is necessary, making this an easy and effective measure to put in place in almost all countries with an active pharmaceutical industry.

⁴³ Akiko Hori (2011). Pharmacovigilance Activities in Japan, Pharmacovigilance: The Study of Adverse Drug Reactions and Related Problems. WHO Collaborating Centre for International Drug Monitoring Uppsala, Sweden.

⁴⁴ JPMA (2001). One Year after “Early Post-marketing Phase Vigilance Surveillance”. Japan: Japan Pharmaceutical Manufacturers Association.



CASE STUDY 6

IT systems and reporting databases for vaccines reporting

Ensuring that the necessary infrastructure for reporting is extensive and intuitive greatly facilitates ADR submissions. Databases and tracking systems can help collect and follow ADRs over a large population which is essential for large scale distribution of biotherapeutics such as vaccines.

Indonesia's Vaccine Adverse Event Reporting System

MOTIVATION

When PV regulation was first implemented, ADRs were communicated by post or email, causing large build-ups, queues, and lags. Companies were required to report in just one format and the volumes of emails sent were quite large.⁴⁵

APPLICATION

Indonesia implemented a database system to record AEFIs called the Vaccine Reporting System (VRS). Under the VRS, the requirements for

vaccines are quite stringent relative to other products in terms of deadlines for reporting. The key difference between the VRS and normal ADR reporting is essentially the time difference.⁴⁶

SUCCESSSES AND CHALLENGES

Although the government has gone beyond the common WHO standard by implementing the VRS, in practice, Indonesia still faces challenges in ensuring HCPs use the system and the PV Unit perceives reporting rates

as low.⁴⁷ There are still issues when reporting through industry as the system was set up fairly recently and there are lots of fields that need to be completed.

TRANSFERABILITY

It is not inexpensive to develop a national database and additionally provide national training for HCPs, industry, and hospitals. Therefore the costs of such a program are likely high. However, the initiative was encouraged and partly funded by WHO.

⁴⁵ Interview with PV Director at Pfizer Indonesia (2015).

⁴⁶ Ibid.

⁴⁷ Ibid.



CASE STUDY 7

Monitoring drug safety with patient registries

It is often difficult with biotherapeutic medicines to fully appreciate the underlying cause of the relevant ADR. The development of a registry of patients in a particular clinical setting provides reliable estimates of the incidence of adverse events across defined populations.

The BIOBADASER / BIOBADAMERICA registry in Brazil

MOTIVATION

As more biotherapeutic treatments came to market, Spanish HCPs noticed higher rates of allergic reactions, severe infections, and potential long-term safety threats when using these treatments. However, there was no consensus concerning the follow-up of ADR. In response, a registry was created to provide information on the safety and effectiveness of these medications to complement established drug monitoring systems.⁴⁸

APPLICATION

In 2000, Spain launched the BIOBADASER register to actively collect information on relevant adverse events

occurring with long-term treatment with biologic therapies.⁴⁹ The registry includes any patients who were treated with a biotherapeutic agent and have rheumatic disease and relies on a control group for estimating the risk of adverse events in similar patients, not just the general population. BIOBADASER has spread as a template for other registries in other countries as well. In 2007, several Latin America countries replicated the register locally, called BIOBADAMERICA.⁵⁰

SUCCESSSES AND CHALLENGES

BIOBADAMERICA and other registries have been used to compare the risks of adverse effects of medicines across

countries and continents.

However, participation is irregular across countries, since many nations do not have the infrastructure or regulatory framework necessary for a fully effective system.

TRANSFERABILITY

The transferability of BIOBADASER to Latin America through BIOBADAMERICA demonstrated that registries can be shared and successfully implemented in other places. However, the unequal and sporadic application of the program in each country highlights that a certain degree of internal infrastructure is necessary for registries to function successfully.

⁴⁸ BIOBADASER (2008). Project Background. <https://biobadaser.ser.es/biobadaser/protocolo/eng/i.html>

⁴⁹ BIOBADASER (2008). Welcome. <https://biobadaser.ser.es/biobadaser/eng/index.html>

⁵⁰ Carmona, L. et al. (2014). BIOBADASER, BIOBADAMERICA, and BIOBADADERM: safety registers sharing commonalities across diseases and countries. *Clinical and Experimental Rheumatology*, 32 (85).

CASE STUDY 8

Minimum standards for PV through harmonization

The introduction of minimum standards can be very beneficial to enhance the collection and report of necessary data associated with the use of biotherapeutic medicines. The harmonization of standards across a whole region could enable information to be gathered more effectively for the more complex use of biotherapeutics.

Establishing minimum standards for PV in SADC

MOTIVATION

SADC countries have adopted biotherapeutics at very different rates and are aware of the additional PV challenges associated with them. The SADC have come to the conclusion that there would potentially be a great benefit in 'harmonizing' their PV systems (i.e. create a collective minimum standard).⁵¹

APPLICATION

The SADC is undertaking a campaign to 'harmonize' the PV systems across

all SADC countries by introducing a 'minimum standard'. This is somewhat similar to the creation of Good Pharmacovigilance Practices (GVP) which were a set of measures drawn up to facilitate the performance of pharmacovigilance in the EU.⁵²

SUCCESSES AND CHALLENGES

Since the introduction of the harmonization, countries have progressed from one category to the next.⁵³ For example, Mozambique, at the lower level, is on

the verge of being classified in the testing level (or the middle level). The expectation/objective is that all SADC countries will be in the upper level by 2019.

TRANSFERABILITY

Similar efforts to introduce minimum PV standards at a regional level can be observed in the Eastern Mediterranean Region of WHO (EMRO) and several countries, namely Sudan, Saudi Arabia, Egypt, and the United Arab Emirates, have initiated joint efforts to harmonize PV activities in the region.⁵⁴

⁵¹ Interview with SADC (2015).

⁵² EMA, Good pharmacovigilance practices, Guidelines on GVP, available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000345.jsp

⁵³ Interview with SADC (2015).

⁵⁴ Ibid.



CASE STUDY 9

Increased safety and efficacy requirements to facilitate PV

Biotherapeutic medicines are commonly used by a small patient population which implies that reporting and monitoring requires a certain level of granularity, sensitivity, and targeted monitoring for appropriate signal detection.

To achieve this, some countries and regions have started to implement universal minimum requirements for PV.

Enhanced monitoring requirement for biotherapeutic medicines in Turkey

MOTIVATION

Reporting of ADRs has remained considerably lower in Turkey than comparable markets, and the Turkish Pharmacovigilance Centre (TUFAM) needed new strategies to highlight the importance of ADR reporting and prioritize reporting of certain products with high-risk profiles.

APPLICATION

In April 2014, Turkey implemented an “additional monitoring list” to encourage more intensive observation of high-risk drugs, which include all biotherapeutic

medicines in order to further clarify the risk profile of drugs in clinical practice. Medicines on this list are marked with a black inverted triangle displayed on the drug’s packaging and Turkey has also recently introduced a pilot project in some hospitals to supplement the additional monitoring list.⁵⁵

SUCCESSSES AND CHALLENGES

One problem with any kind of additional monitoring list is the same factors that contribute to underreporting in other areas of PV will still affect the drugs on the additional monitoring lists, even if

more stringent labelling requirements raise some awareness. This is why it is especially interesting that Turkey has paired the additional monitoring list with active hospital observation programs.

TRANSFERABILITY

Considering that this program is already present in the EU and in its infancy in the Arab League, it is feasible that additional monitoring programs could be implemented in other countries around the world. A good part of the regulatory burden falls on pharmaceutical companies that must meet new standards of labelling and packaging their products.

CASE STUDY 10

Additional monitoring requirement for biotherapeutics

To address some of the challenges associated with biotherapeutic medicines, regulatory authorities around the world have developed increased safety and efficacy requirements to facilitate PV for biotherapeutics and vaccines such as the introduction of Risk Management Plans (RMP) or Periodic Safety Update reports (PSUR).

Tailoring of PV requirements to local need in Egypt

MOTIVATION

One important challenge of PV in Egypt has been linked to upgrading the set of capabilities and skills necessary to ensure the adequate monitoring, reporting and collection of data at local level.

APPLICATION

In January 2012, the EPVC released the final version of Egyptian guidelines for Pharmacovigilance for Human Pharmaceutical products (Drugs and Biologicals) requiring the Marketing Authorization Holder (MAH) or its representative in Egypt to ensure that

it has an appropriate system of PV and risk management in place in order to fulfil Egypt-specific PV requirements.⁵⁶

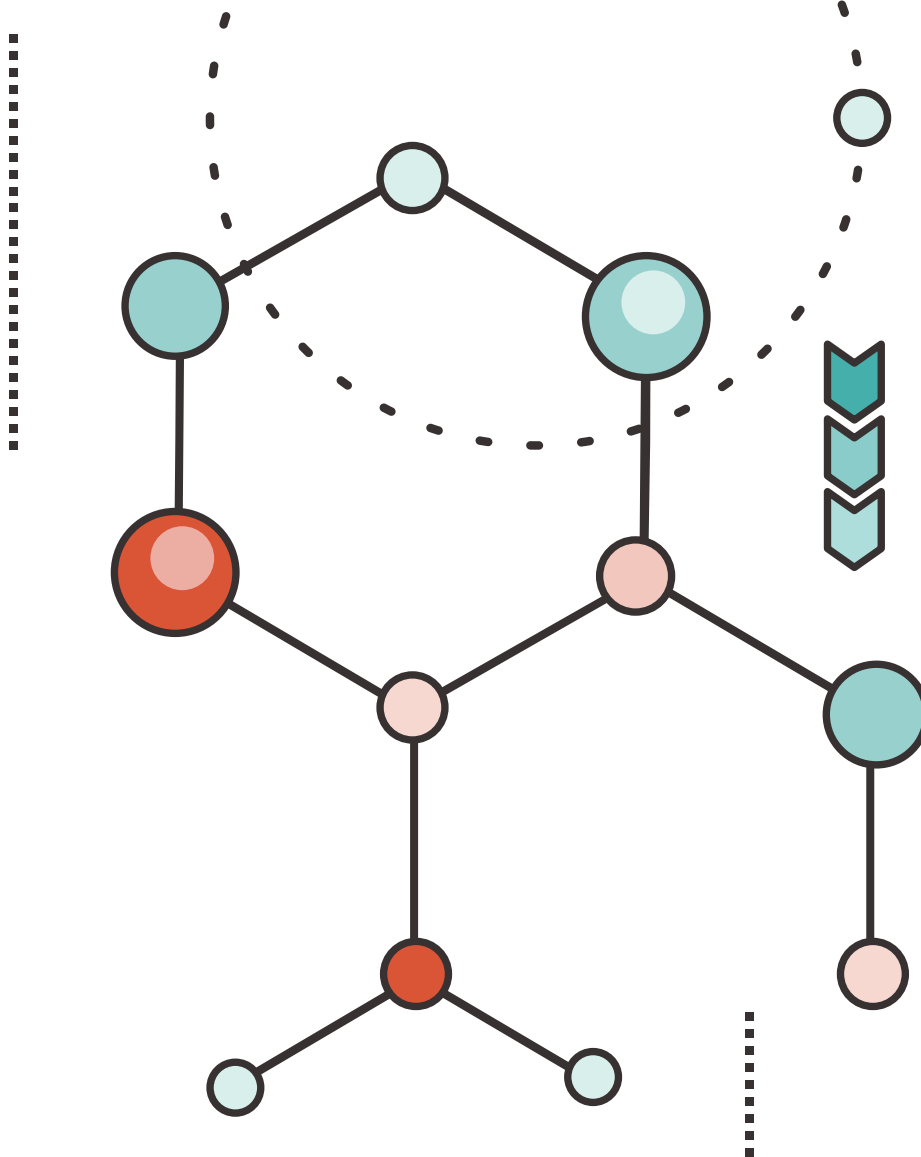
SUCCESSES AND CHALLENGES

The development of local PV guidelines encourages small local companies to upgrade their PV capabilities and multinational companies operating in Egypt to develop local capabilities. Companies are starting to pay more attention to local requirements and have brought the attention of their headquarters to them by hiring dedicated local staff for PV.

TRANSFERABILITY

Since 2001, the EPVC is a member of the WHO International Drug Monitoring Programme (Uppsala Monitoring Centre - UMC) who has provided support and EPVC guidelines and SOPs. Both the Egyptian PV guideline and subsequently the Arab League guidelines have largely adopted existing Good Pharmacovigilance Practices (e.g. the EU's GVP) which was assessed against local need and considered the most compatible with the Egyptian PV environment.

⁵⁶ Egyptian Drug Authority (2012) Egyptian Guideline for Marketing Authorization Holders (MAHs) Guidelines on Pharmacovigilance for Medicinal Products for Human Use, The Egyptian Pharmacovigilance Center (EPVC).



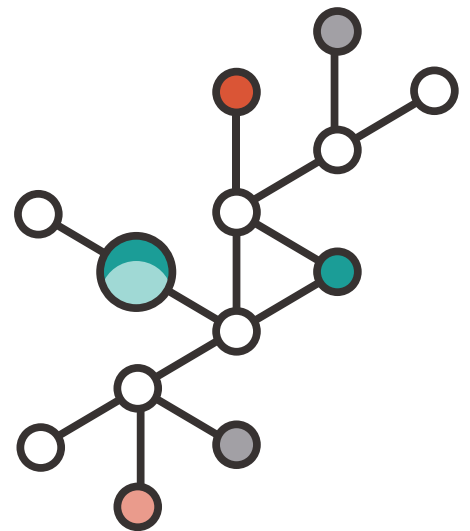
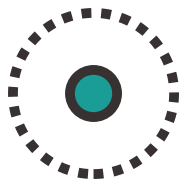
STAY CONNECTED

Learn more and stay connected



www.ifpma.org

Chemin des Mines 9
P.O. Box 195
1211 Geneva 20
Switzerland



IFPMA represents the research-based biopharmaceutical companies and associations across the globe. The research-based biopharmaceutical industry's 2 million employees research, develop and provide medicines and vaccines that improve the life of patients worldwide. Based in Geneva, IFPMA has official relations with the United Nations and contributes industry expertise to help the global health community find solutions that improve global health.

IFPMA manages global initiatives including: *IFPMA Developing World Health Partnerships* initiative studies and identifies trends for the research-based pharmaceutical industry's long-term partnership programs to improve health in developing countries and the *IFPMA Code of Practice* sets standards for ethical promotion of medicines.





IFPMA

www.ifpma.org

Chemin des Mines 9

P.O. Box 195

1211 Geneva 20

Switzerland

