International Federation
of Pharmaceutical
Manufacturers & Associations

Pharmacovigilance

Good Pharmacovigilance Principles and Considerations for Biotherapeutic Medicines

IFPMA

Contents

Pharmacovigilance: Reasons for Reading On

Everyone should understand the value in reporting side effects of medicines. This is an important measure by which the safety of medicines for, and treatment of patients worldwide can be improved. Less is further known about how reporting actually happens, what may prevent reporting from happening effectively and what is done with the data once collected. Collectively, these activities are referred to as pharmacovigilance (PV), and we all have a role to play in delivering effective PV.

In order to anticipate, identify, record and report side effects, we first need to have a good understanding of the medicines themselves. Biotherapeutic medicines (or biotherapeutics) are complex and have unique characteristics; therefore they require appropriate PV monitoring. The purpose of this brochure is to help outline the challenges, explain how PV practices can address these challenges and describe the different roles we all have in contributing to effective monitoring for safe medicines use.

1 Pharmacovigilance and Biotherapeutic Medicine

The World Health Organization (WHO) describes "pharmacovigilance" as "the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem."[1] PV systems are widely recognized as important tools in the regulatory process for medicines, for protecting public health and an integral component of patient healthcare. The WHO describes a national PV system "as an obligatory investment in the future public health of the territory."[2]

It is impossible to completely characterize the safety profile of a new medicine through clinical investigations before the first marketing authorization is granted. PV is necessary as it allows health authorities to continue to assess benefit/risk throughout the life-cycle of a medicine and potentially detect rare and serious adverse drug reactions (ADRs) that were not detected before marketing authorization. PV can also identify new safety signals related to product quality and/or changes in use and prescription patterns. In order to do so it is important that a robust national PV system is established.

However, maintaining a robust PV system relies on consistent and accurate acquisition, integration and analysis of ADR data.[3,4] Without such a strong foundation important safety signals can get hidden, confounded or diluted. Moreover for any given medicine used across the globe, it is imperative that ADRs are collected, safety signals identified and analyzed in a comprehensive way, combining the output from multiple national PV systems. To that end, the WHO Program for International Drug Monitoring was set up in 1978 and is delivered by the Uppsala Monitoring Centre.[5]

To provide some context for what this means in practical terms, the European Commission has defined the following expectation for EU Member States to enact at the national level:

European Commission Directive 2010/84/EU:[6]

(e) ensure, through the methods for collecting information and where necessary through the follow-up of suspected adverse reaction reports, that all appropriate measures are taken to identify clearly any biological medicinal product prescribed, dispensed, or sold in their territory which is the subject of a suspected adverse reaction report, with due regard to the name of the medicinal product, in accordance with Article 1(20), and the batch number;

[1] WHO (2014) Essential Medicines and Health Products: Pharmacovigilance. World Health Organization, February 3, 2014 [online]. http://www.who.int/medicines/areas/quality_safety/safety_efficacy/pharmvigi/en/

[2] The Safety of Medicines in Public Health Programmes: Pharmacovigilance an essential tool, 2006.

[3] The WHO has created guidelines for pharmacovigilance systems that can be found through the following link: http://www.who.int/medicines/areas/quality_safety/safety_efficacy/Pharmacovigilance_B.pdf

[4] WHO has also endorsed a web-based toolkit, developed by pharmacovigilance experts, reviewed by the Uppsala Monitoring Centre and funded by the Global Fund, that can be found through the following link: http://pvtoolkit.org/

[5] "As of October 2013, 117 countries have joined the WHO Programme for International Drug Monitoring, and in addition 30 'associate members' are awaiting full membership while compatibility between the national and international reporting formats is being established." World Health Organization, February 3, 2014 [online]. http://www.who-umc.org/DynPage.aspx?id=98080&mn1=7347&mn2=7252&mn3=7322&mn4=7324

[6] The European Parliament and the Council of the European Union (2010) Directive 2010/84/EU of the European Parliament and of the Council. The European Parliament and the Council of the European Union, January 6, 2015 [online]. http://ec.europa.eu/health/files/eudralex/vol-1/dir_2010_84/dir_2010_84_en.pdf

While this need for a strong foundation is common to all medicines, it is especially so for biotherapeutic medicines.[7,8] The specific characteristics of such complex products immunogenic potential require more emphasis on PV monitoring. Regulators in the European Union (EU) have put mechanisms in place to strengthen PV monitoring to ensure accurate attribution of ADRs and the medicinal product.[9] The United States Food and Drug Administration (US FDA) has made similar suggestions in their draft biosimilar guidance issued in February 2012.[10]

A recent discussion on PV for biotherapeutic medicines at the Brookings Institution in Washington D.C. summarized the imperative: "PV systems depend on the accurate identification of individual products and an ability to link exposure to possible adverse outcomes."[11] This challenge becomes more difficult in a global environment with multiple sources of a given class of biotherapeutic medicine, including biosimilars and other biotherapeutics that have been authorized under different regulatory pathways. Product-level traceability is a core objective for PV systems for biotherapeutics medicines; the challenge is how to achieve this within countries and how to connect these systems globally so that safety signals are quickly and correctly identified and assessed.

[7] Giezen et al. Safety-Related Regulatory Actions for Biologicals Approved in the United States and the European Union. JAMA, 2008; 300(16): 1887

[8] Giezen, T., et al. (2009). Pharmacovigilance of Biopharmaceuticals. Drug Safety 32(10): 811-817.

[9] Regulation (EU) No 1235/2010 of the European Parliament and of the Council of 15 December 2010. Official Journal of the European Union. 2010;348:1-16; Directive 2010/84/EU of the European Parliament and of the Council of 15 December 2010 amending, as regards pharmacovigilance, Directive 2001/83/EC on the Community code relating to medicinal products for human use.

[10] FDA. Guidance for Industry. Scientific considerations in demonstrating biosimilarity to a reference product (February 2012); section VIII.

[11] Engelberg Center for Health Care Reform at Brookings, Developing Systems to Support Pharmacovigilance of Biologic Products: Discussion Guide (Nov. 15, 2013) (Brookings Paper).

Key Principles

• All medicines have the potential to cause ADRs. Biotherapeutic medicines have unique product characteristics, due to their biological nature and complex structure that require individual product ADR tracking. Certain events which may be too rare to be detectable during clinical trials prior to the marketing authorization can lead to ADRs or even decreased efficacy.

2 Importance of Traceability for Biotherapeutic Medicines

As highlighted in the previous section, accurate identification of an individual biotherapeutic medicine and manufactured batch is one of the pillars of a good PV system. Because of their complexity, biotherapeutics may cause unwanted immune responses, which differ in range and severity and sometimes are difficult to identify quickly. The complex production process of a biotherapeutic partly determines the characteristics of the end product, and this process is tightly controlled for consistency. When changes occur in the process, either intentionally or unintentionally, this has the potential for triggering ADRs, which can occur up to many months after initiation of treatment. Therefore, more than for conventional chemically-synthesized small molecule medicines, post-approval follow-up on an individual product level is essential. Full traceability requires not only that the ADR report can be allocated to one particular biotherapeutic medicine and given batch, but also that it is verifiable that this is indeed the same product that was originally dispensed to the patient (see *Figure 1*).

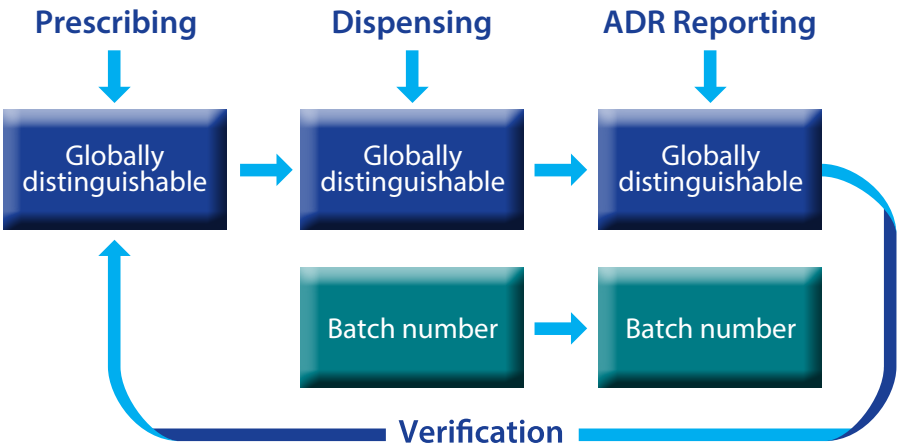
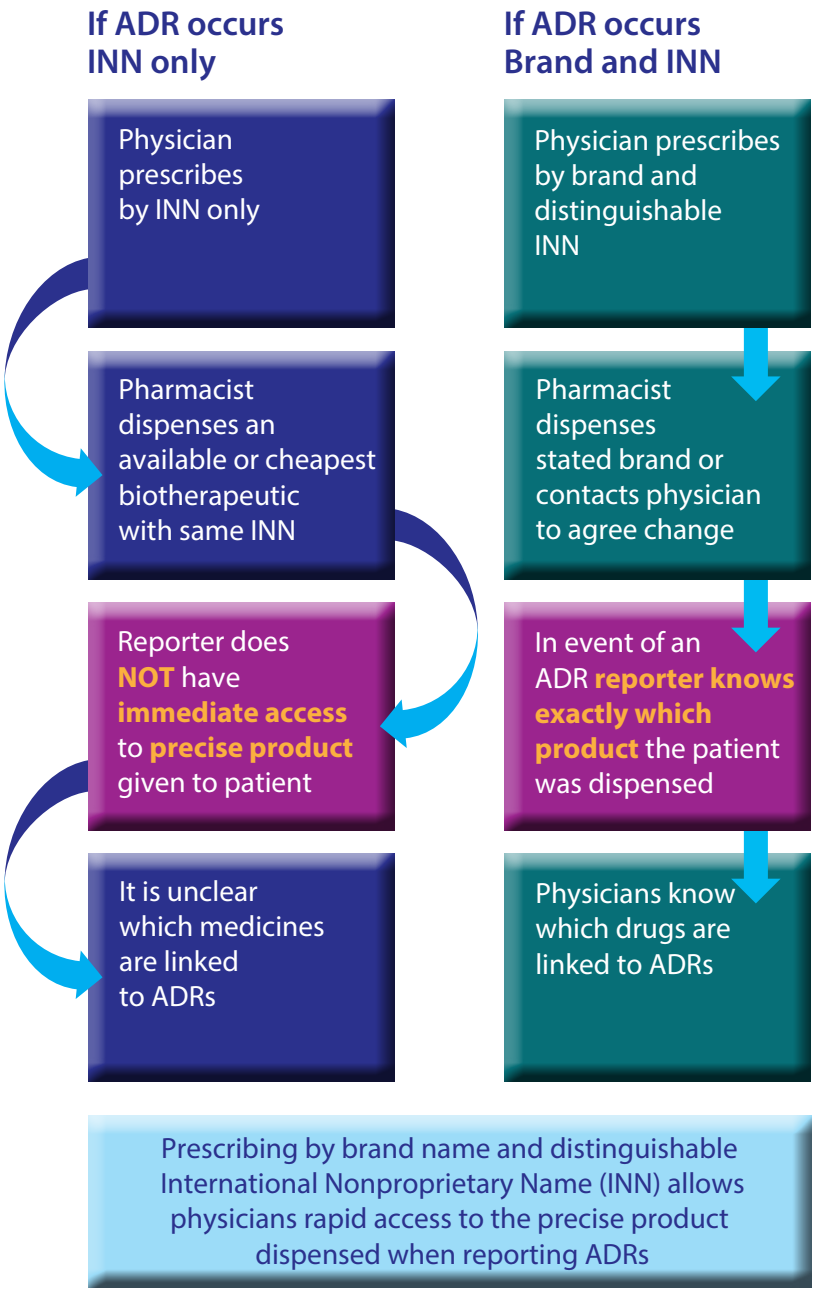


Figure 1: Full traceability throughout the prescribing, dispensing and ADR reporting chain

To achieve product-level traceability for biotherapeutics, clear identification and recording is needed. A fundamental measure for identification is the use of a distinguishable name, which is used consistently around the world and yet unique for each individual biotherapeutic medicine. Batch number is also an important identifier for traceability, and has proven particularly useful for identifying batch-related ADR to a product belonging to one Marketing Authorization Holder (MAH). However, recent experience in some regions demonstrates that batch numbers are not as frequently recorded in ADR reports.[12] Therefore, additional means of identification and recording are needed at all steps of use: through prescription, dispensation, record-keeping, ADR reporting and signal analysis to ensure that a link can be made between an ADR reported in any jurisdiction and the exact product dispensed to that patient.

[12] Vermeer, N., et al. (2013). Traceability of Biopharmaceuticals in Spontaneous Reporting Systems: A Cross-Sectional Study in the FDA Adverse Event Reporting System (FAERS) and EudraVigilance Databases. Drug Safety 36(8): 617-625.



Source: Amgen

Figure 2: In a multisource environment, distinguishable names ensure traceability

Loss of traceability can occur for a number of reasons. An example is given in *Figure 2*. *Figure 2* describes the impact when a medicine is prescribed in an environment where separate products are marketed using the same non-proprietary name and the physicians and pharmacists do not record a distinguishable name for what is prescribed and dispensed. Subsequently a reporter, who could be the prescriber or patient, needs to associate a side effect with the drug dispensed and report to a company or national regulatory agency (NRA).

Key Principles

- **Each biotherapeutic medicine including biosimilars should be required to have a distinguishable name that clearly differentiates it from other biotherapeutic medicines. This will ensure clear identification, safe prescription and dispensing to patients, and enable accurate reporting and analysis of ADR data (i.e., improve traceability).**
- **It is very important that healthcare professionals are educated and encouraged to use the distinguishable name when prescribing and dispensing to ensure that any ADRs reported are assigned to the correct biotherapeutic medicine and batch number.**

ADR Collection and Signal Detection

A second important pillar of PV is the ability to link exposure to possible adverse outcomes.[13] This is done through a process called signal detection. As described previously, the ability to conduct PV is an important tool for health authorities to continuously assess the benefit/risk throughout the lifecycle of a medicine. Product development and subsequent authorization aims at making medicinal products available that have been demonstrated to be effective and safe. At the same time, however, it is important to ensure that medicines are made available as quickly as possible to patients that need them. There needs to be a good balance between the amount and type of data (e.g. survival data, pharmacodynamic endpoint) that need to be available prior to authorization and the data that can be generated after approval (e.g. higher number of patient exposure). With increasing complexity of the products involved, this balancing act becomes more important, recognizing that clinical studies during the development of a medicine will never be able to fully provide certainty. Thus, national regulatory agencies (or regulators) and industry are constantly looking for more risk-based approaches that allow earlier access while still ensuring adequate efficacy and safety. Such approaches rely on additional data being generated post-marketing authorization approval to inform on defined and acknowledged uncertainties remaining at the time of marketing approval and to confirm the benefit/risk profile in clinical practice.

Because of the variety and rarity of ADRs that can be anticipated for biotherapeutic medicines, PV systems need to be suitably sensitive to identify changes in ADRs with respect to incidence, type and severity and to be able to correctly link these signals to products. Several PV techniques are available, spontaneous reporting of ADRs being the most widely and globally used. Other, more complex methods such as medical registries or retrospective analyses of existing databases can be used in addition, to focus on a certain product (class) or on an event. Many products of biological origin, especially those intended for serious diseases, use registries to follow the patient population in more detail.

The most widely used method of PV relies on spontaneous reporting of suspected ADRs and many important safety signals have been picked up in this way. Drawbacks of spontaneous reporting include underreporting, incomplete information, and sensitivity to known or unknown external factors.[14] Furthermore, the vast number of spontaneous reports received makes case-by-case analysis and medical evaluation more and more challenging and specific tools have therefore been developed to

[13] Engelberg Center for Health Care Reform at Brookings, Developing Systems to Support Pharmacovigilance of Biologic Products: Discussion Guide (Nov. 15, 2013) (Brookings Paper).

[14] The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP). Guide on Methodological Standards in Pharmacoepidemiology (Revision 1).

help identify patterns in the data (e.g. disproportionality analysis).[15,16] To facilitate aggregated analysis of the data, spontaneous ADR reports are collected in databases. However, these databases may have some limitations too (e.g. reporting practices of the countries that submit the data to the database may differ considerably or time difference between the occurrence of the event and the availability in the database).

Example of Databases

WHO International Drug Monitoring Program Vigibase
http://www.umc-products.com/DynPage.aspx?id=73590&mn1=1107&mn2=1132

US FDA ADR Reporting System for Pharmaceutical Products (FAERS)
http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm

Eudravigilance Database in the EU
https://eudravigilance.ema.europa.eu/highres.htm

A *registry* is an organized system that uses observational methods to collect uniform data on specified outcomes in a population defined by a particular disease, condition or exposure.[17] Ideally a registry will contain a control group and should not only include patients being prescribed a specific product. As for spontaneously reported data, in practice, recorded data can be inaccurate or incomplete. Furthermore, participation in a registry is voluntary and will vary by practice or institution. Registries do not stand on their own; they are used as a data source within which (epidemiological) studies can be performed, keeping in mind guidelines for good pharmacoepidemiology. In addition, ADRs reported in a registry will also be dealt with as spontaneous reports and end up in one of the databases described above.

Whether signals originate from the monitoring of data from spontaneous reporting or from data originating from other sources can be based on a number of ADRs received over a defined period of time for a defined drug substance or medicinal product. Higher reporting than expected for the active substance or product of interest is considered to be a signal, which has to be further investigated and validated. The 'expected' reporting rate can be related to all other active substances/medicinal products in the database. The principles of these calculations are shown in *Figure 3*. The larger the database, the more representative the 'expected' reporting rate will be. But it can also be easily seen from this figure that misclassification of one or more ADRs can lead to a substantial shift outcome, which could make the difference between a signal or no signal, in particular when the ADR is rare.

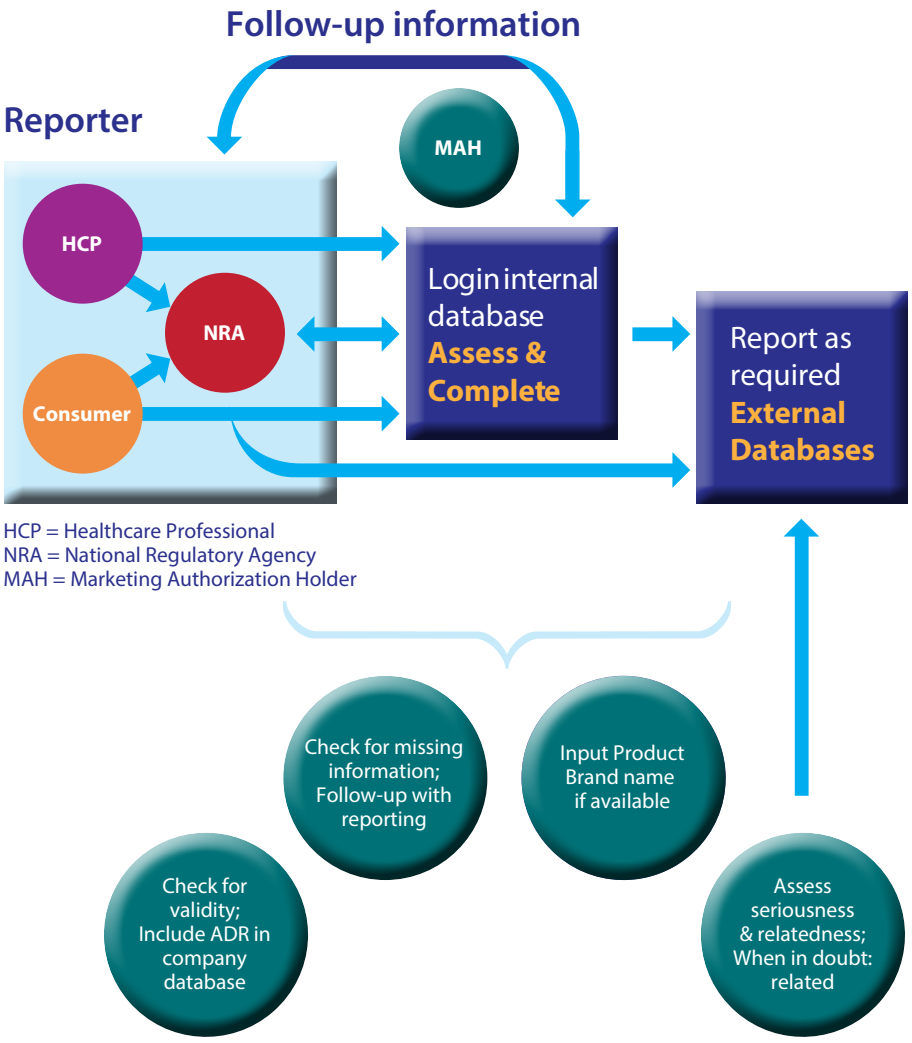
[15] Almenoff JS, Pattishall EN, Gibbs TG, DuMouchel W, Evans SJW, Yuen N. Novel statistical tools for monitoring the safety of marketed drugs. Clin Pharmacol Ther 2007;82:157-66.

[16] The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP). Guide on Methodological Standards in Pharmacoepidemiology (Revision 1).

[17] Guideline on Good Pharmacovigilance Practices (GVP) – Module V, EMA/838713/2001.

Key Principles

- **PV reporting systems should be easy to use to allow reporting by any party including patients and HCPs and well-structured to facilitate the meaningful analysis of ADR data on biotherapeutic medicines.**
- **Health authorities, national regulatory agencies, medical researchers and companies should be able to perform analyses at both the product class (e.g. epoetin) and individual product level (i.e. separated by manufacturer or MAH) for each biotherapeutic medicine.**



Source: MSD

Figure 3: Reporting path of and ADR from reporter to final database

If an unexpected ADR with a particular product does occur, early signal detection and subsequent rapid assessment and validation are important. This will allow quick and targeted action (e.g. risk minimization through a change in the product information, communications to healthcare professionals (HCPs) or even a temporary withdrawal of the product from the market). The longer it takes to pick up the signal, the more patients will have been exposed and be at risk. When searching for signals, therefore, the limitations of the dataset play a role to determine the evidentiary value. For these reasons, signal detection should follow recognized and robust methodology and a multidisciplinary approach, including statistical analysis that is appropriate for the data set. Proof of causality will always require additional evidence to be generated.

Risk Management Plans and Risk Minimization Elements in the PV System

At the time of regulatory approval, the safety information about a medicine is still relatively limited compared to the information that will be available when the medicine is actually used in healthcare practice over the years. The evidence compiled for regulatory approval may identify known or potential safety risks for patients, based on the preclinical and/or clinical study results. There may also be missing information, which is defined as "critical gaps in knowledge for specific safety issues or populations that use the marketed product"[18].

The company responsible for a biotherapeutic medicine usually agrees with the approving regulatory authority on a safety plan, known as a risk management plan (RMP), to address this need to further collect and analyze the safety data for a given medicine – its known and potential risks and any missing information.

The European Medicines Agency (EMA) recently summarized the scope of a RMP as a defined set of PV activities which:

- Aim to characterize the safety profile of the medicine
- Proactively plan activities to characterize risks and to identify new risks and increase knowledge about the safety profile of the medicine; and
- Plan and implement risk minimization and mitigation and to assess the effectiveness of these efforts.[19]

In many countries, RMPs are a requirement for marketing authorization, and it is expected that the RMP will be continually modified and updated as the PV work proceeds and safety data is gathered and assessed.

[18] Annex IV, ICH-E2C(R2) Guideline.

[19] Guideline on Good Pharmacovigilance Practices (GVP) – Module V, EMA/838713/2001.

Key Principles

• IFPMA supports pro-active management of potential risks to further mitigate adverse consequences to patients. For effective RMP, an effective system for identification of medicines, clear prescribing and recording of the information, and good communication to HCPs, patients and their carers are needed.

RMP and risk mitigation applies to all medicines, but for biotherapeutics, including biosimilars, there is the added emphasis for monitoring because the safety profile of these medicines is sensitive to seemingly small changes in production processes, while any problems identified after approval are often related to impacts to the immune system resulting from the treatment.[20] Risk mitigation measures may include educational materials and programs including registries.

Furthermore, considerable effort is needed in not only engaging HCPs, patients and their carers in understanding their role in risk management, but also to explain why risk management is needed and how these safety risks should be considered in the context of their treatment.[21]

To encourage patients and HCPs to report any ADRs through their national reporting systems, and thereby to help support global safety signal identification and analysis, some countries and regions have instituted specific monitoring requirements for newly approved active substances and for all biotherapeutic medicines, including biosimilars.[22]

The success of a RMP relies on the possibility to quickly identify potential problems and therewith on an effective system for identification of medicines, clear prescribing and recording of the information, and this needs to be well communicated to HCPs, patients and their carers.

[20] Giezen, T. J., et al. (2008). "Safety-Related Regulatory Actions for Biologicals Approved in the United States and the European Union." Journal of the American Medical Association (JAMA) 300(16): 1887-1896.

[21] Edwards IR, Lindquist M. Understanding and Communicating Key Concepts in Risk Management: What do we mean by Benefit and Risk? Drug Safety, 2009, 32(6):449-452.

[22] For example, the European Union now requires a special symbol for newly approved active substances and for biologics, including biosimilars, authorised after 1 January 2011 to be included on package. For further details please see European Commission. Pharmaceuticals: New symbol to identify medicines undergoing additional monitoring. European Commission, April 19, 2013 [online]. http://europa.eu/rapid/press-release_IP-13-199_en.htm?locale=en

5 Roles and Responsibilities of Stakeholders

The global diversity in the organization of public health systems means that many countries lack the necessary facilities, expertise and resources for PV.[23] Primary healthcare may not be delivered by medically-trained personnel but rather by trained non-medical village workers with incomplete understanding of adverse reactions. Shortages of resources may lead to underdeveloped medical control systems and lack of laboratory facilities to help diagnose ADRs. Public Health Programs (PHPs) or Patient Support Programs (PSPs) may exist, based on direct administration of medicines, either directly controlled by the country, or under the leadership of an international organization such as WHO or UNICEF. Also in such programs, patients rarely have direct contact with a physician, as resources are usually focused on setting up the program.

Where PV systems and PHPs exist alongside each other, this may lead to duplication of effort and lack of harmonization in terminology, data collection and causality assessment. Depending on the country, national PV centers may be centralized or decentralized and function at different levels (district, state or country level). Whatever the structure, it is important to ensure good coordination, bringing the relevant expertise together and integrating the PV activity between the different vertical structures (disease specific PHPs or other systems) in a country or region together.

For effective PV, global standards and guidelines are needed as well as free exchange of information regarding ADRs on a local, regional or global level. Such exchange has been made easier by the standardization of the minimum criteria for a meaningful adverse reaction report and the WHO Program for International Drug Monitoring at the Uppsala Monitoring Centre has been central to this effort. The objective now is to extend this further and to provide further guidance and direction with respect to biotherapeutic medicines.

Even the best designed PV system is meaningless without the contributions of all stakeholders (regulators, MAHs, HCPs, patients and their carers and the wider public) (see *Figure 4*) to provide the information about a medicine and any potential impact on safety. The responsibilities of each of the stakeholders in the risk management cycle have been highlighted below, with special reference to biotherapeutics.

Figure 4: Key stakeholders

[23] WHO. The Safety of Medicines in Public Health Programmes. Pharmacovigilance an Essential Tool.

MAHs (Marketing Authorization Holders)

MAHs are the 'owner' of a medicinal product and as such primarily responsible for ensuring that the objectives for PV are being met and that appropriate action can be taken when needed. In many jurisdictions, this responsibility is captured in the law.

With respect to biotherapeutics, MAHs should provide clinical immunology and analytical support to HCPs and patients to help them to identify and manage related ADRs.

MAHs

MAHs, usually through a qualified person for PV, are responsible for:

- Continuous monitoring of PV data and scientific evaluation of all information on the risks of the medicinal product.
- Submission of accurate and verifiable data on ADRs to the competent authority.
- Effective communication with the competent authority on any information that may impact the benefit/risk balance.
- Update of the *product information* to reflect all scientific knowledge and communication of relevant safety information to HCPs and patients.

Regulators

The regulators have a dual role in PV activities. On the one hand, they supervise the compliance of applicants with their PV activities.

On the other hand, they play a role in facilitating PV activities in their territory (e.g. by facilitating reporting of ADRs or by creating databases that allow pooling of data to facilitate analysis). They can also play a role in proactive safety reviews and data capture that can be organized for cohort event monitoring, linked to a particular healthcare investment or initiative. Such examples are evident for healthcare programs initiated by WHO and other non-governmental organizations and charities.[24]

For biotherapeutics, regulators should also provide guidance and support to HCPs and patients to help them to identify and report ADRs, advising specifically on the need for product-specific identifiers, including batch numbers. With respect to process changes for biotherapeutics, the regulators closely assess these changes for impact on safety and efficacy and monitor the results accordingly. Because substitution of one biotherapeutic medicine for another in the course of a patient's treatment requires careful consideration of the patient's individual circumstances, the regulator and health authority should encourage the HCPs to carefully consider and document the substitution to ensure accurate traceability. Moreover, guidance regarding substitution between products, including between biosimilars and their reference products, should be provided to ensure that these products are not used interchangeably without evidence supporting a lack of impact on patient safety or efficacy.

An efficient and direct way to provide HCPs with essential information is to include such information and guidance in the labelling of the medicine. More generally, common communication methods and templates could facilitate more effective recording and reporting of adverse events and proactive risk management.

Regulators

Regulators will organize PV inspections to ensure that:

- The MAH has everything in place that is needed to meet the PV requirements.
- To identify and address non-compliance and take enforcement action when necessary.

[24]For further details on cohort event monitoring and examples, please refer to:
http://www.who.int/hiv/topics/pharmacovigilance/4_pharmacovigilance_cem.pdf

HCPs (Healthcare Professionals)

Spontaneous reporting systems are the most common mechanism by which safety reporting occurs, and these systems rely heavily on the direct contributions of all stakeholders who have been involved in the prescription, delivery and use of a medicine by a patient. This includes physicians, pharmacists or other healthcare workers. Their role is to ensure that the patient is sufficiently informed and motivated to report any untoward effects they may experience. They also have a crucial role in ensuring traceability of the prescribed product by ensuring that all necessary information on the product prescribed and dispensed is included in the patient file, which can be accessed for verification e.g. in case of a reported ADR. For biotherapeutics, these roles and responsibilities remain the same, nevertheless further education and engagement may be helpful in preparing all stakeholders to identify and manage related ADRs.

Patients and their carers

Patients primarily have the responsibility to comply with the treatment schedules and recommendations in the label and to be aware of important risks. Although much of the focus for ADR reporting has been centered on the regulatory authorities, the manufacturers responsible for the medicines themselves and the reporting healthcare practitioner, PV systems are opening up to more direct input from patients themselves as well as other representative bodies. A good understanding by patients of the potential benefits and risks of a medicine is likely to have a positive effect on reporting of ADRs and compliance with suggested risk minimization activities (see *Table 1*).

Availability of batch numbers for reported suspected biopharmaceuticals stratified by type of reporter

Reporter type	FAERS (*n*=487,065)		EV (*n*=356,293)	
	Total number of drugs[a]	Drugs with batch number available [*n*(%)]	Total number of drugs	Drugs with batch number available [*n*(%)]
Physician	112,770	15,026 (13.3)	94,928	6,667 (7.0)
Pharmacist	12,971	2,984 (23.0)	9,999	1,896 (19.0)
Other healthcare professional	64,235	9,087 (14.1)	46,765	5,366 (11.5)
Consumer	198,282	76,006 (36.3)	117,411	47,800 (40.7)
Lawyer	1,489	10 (0.7)	1,242	5 (0.4)

[a] For a total of 97,318 biopharmaceuticals in the FAERS and 85,948 in EV, the reporter type was not unique or unavailable. *EV* Eudra Vigilance, *FAERS* FDA Adverse Event Reporting System

Table 1: Availability of batch numbers for reported suspected biopharmaceuticals stratified by type of reporter [25]

Key Principles

• Even though the clinical effect of certain products may be similar, healthcare professionals should be educated on the necessity for using distinguishable names when prescribing biotherapeutic medicines. This practice will help maintain the role of the physician in selecting a particular therapy for the patient and provide clarity for the pharmacist about what medicine was prescribed.

• Confusion about the physician's intended treatment choice may lead to automatic substitution and inaccurate attribution of ADRs as the prescribing physician may not be aware which medicine the patient received.

• Currently, there is no scientific basis to conclude that greater or lesser rigor in the collection of PV data for biosimilars is required when compared with originator products. Ensuring that all biotechnology manufacturers, adhere to global standards for manufacturing and PV (WHO, ICH, CIOMS,) will protect patient safety and maintain the quality of existing PV practices. Therefore, each MAH of each biological product must have an established PV system to ensure comprehensive monitoring of the product.[26]

[25] Vermeer, N., et al. (2013). "Traceability of Biopharmaceuticals in Spontaneous Reporting Systems: A Cross-Sectional Study in the FDA Adverse Event Reporting System (FAERS) and EudraVigilance Databases". Drug Safety 36(8): 617-625.

[26] WHO http://www.who.int/biologicals/en/; International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use http://www.ich.org/; Council for International Organizations of Medical Sciences http://www.cioms.ch/

6 Global Signal Detection

Global pharmaceutical companies aim to develop and make their products available to patients worldwide. This means that ADRs will be reported in principle from many countries all over the world. In addition, ADRs can be reported by HCPs, regulatory authorities, patients or anyone else who becomes aware of an untoward effect to a certain medicine. To allow correct and timely reporting and analysis of this large variety of data, pharmaceutical companies have set up extensive PV systems. A schematic outline of the path followed by an ADR starting at the reporter and ending with the actual inclusion in the database is given in *Figure 3*.

Minimum criteria have been defined for information that needs to be available in order to have a meaningful case report. Lack of any of these elements means that the case is incomplete. It is the responsibility of the MAH to put every effort into collecting the missing data. However, in practice, the success rate of such follow-up queries is low, while also privacy considerations have to be taken into account.

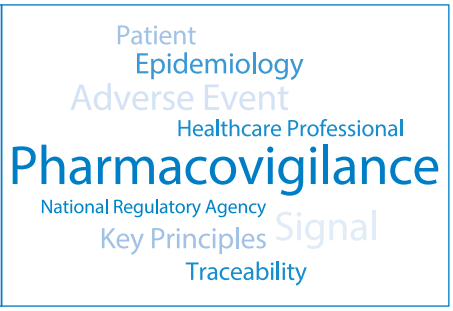
The 4 essential elements for an ADR:

(1) Identifiable reporter

(2) Identifiable patient

(3) Adverse reaction

(4) Suspected product



Both the MAH and the NRA have the task to collect sufficient information to ensure that reports are authentic, accurate, as complete as possible and non-duplicative. Furthermore, a high number of drug-specific ADRs in an adverse reactions database have been shown to increase the power for detecting safety signals.[27] From that perspective, it is beneficial to be able to share and exchange information on adverse reaction reports. Global standards for essential elements in reporting processes and definitions would facilitate the use of global databases for collating and searching data as well as for testing hypotheses once a signal has been detected. Such standards, specifically in relation to the 4 essential elements, can also facilitate the elimination of duplicates (based on identifiable reporter and patient) and avoid misclassifications (e.g. due to imputation of the name of the suspected product when the reported name does not unequivocally identify the individual product). Overall, consistent global processes and use of well-defined standards will increase the quality of the data.

[27] Hammon IW, Gibbs TG, Seifert HA, Rich DS. Database Size and Power to Detect Safety Signals in Pharmacovigilance. Expert Opin Drug Saf 2007;6:713-21.

Summary

Biotherapeutic medicines, including biosimilars, have brought considerable benefits to patients around the world. New biotherapeutic medicines and more alternatives for supply will bring further value to patients and to healthcare systems. However, because of the complexity of biotherapeutic medicines and their unique method of manufacture, a strong PV system is needed to ensure that value is maintained and patient safety remains at the center of our efforts.

Effective PV for biotherapeutics, particularly as multiple sources of biotherapeutics emerge globally, requires that we establish product-level traceability. Some of this will be made possible by advances in non-proprietary identification. However, much of this effort relies upon the effectiveness of PV systems and the practices of safety reporting amongst not only regulators and manufacturers, but critically amongst HCPs, patients and the wider public.

Countries generally have some form of PV system in place, and this has developed in the context of the healthcare setting and needs of that country. However, PV is a global effort, and we support the WHO in its efforts to help countries to further develop their PV systems and practices to reach a common standard and to encourage and support global safety reporting and analysis for the benefit of all patients.

Characteristics of robust PV systems

- Easy to use (reporting forms, procedures for submission and collection of reports)
- Allows reporting by patients and healthcare providers
- Well structured to facilitate analysis
- Standardized procedures and definitions (e.g. what is a reportable event, follow-up and processing of case reports)
- Allows analysis on product class level (e.g. epoetin) and on individual product level (by manufacturer or MAH)
- Procedures for analysis of aggregated information
- Good communication practices
- Training

Collaboration is key

Greater engagement in and support for PV practices are needed to empower all stakeholders to help deliver effective safety reporting on a global basis. Good practices exist in many countries, but in too many settings, patients, HCPs and other stakeholders do not understand the role that they should play or feel concerned that they will not be well received by the authorities if they raise safety concerns. The EMA recognizes this important measure, and it will soon be publishing its first "Good Vigilance Practice" Module (XI) on public participation in PV. This is a trend that must become global if we are to ensure that the effective PV systems we establish, have the critical input of safety information provided by all stakeholders – our critical partners for PV.

Glossary

Adverse (Drug) Reaction (ADR): A response which is noxious and unintended, and which occurs at doses normally used in humans for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function. (WHO, 1972).

An ADR, contrary to an adverse event, is characterized by the suspicion of a causal relationship between the drug and the occurrence, i.e. judged as being at least possibly related to treatment by the reporting or a reviewing health professional.[28]

Adverse Event (AE): Any untoward medical occurrence that may present during treatment with a pharmaceutical product but which does not necessarily have a causal relationship with this treatment.[29]

Biotherapeutic Medicines: Medicines whose active ingredients are or are derived from proteins (such as growth hormone, insulin, antibodies) and other substances produced by living organisms (such as cells, viruses and bacteria). They are larger and more complex than chemically synthesized drugs and their characteristics and properties are typically dependent on the manufacturing process itself.[30]

Drug Substance: An active ingredient that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure or any function of the human body, does not include intermediates used in the synthesis of such ingredient (21 CFR 314.3(b)). The term *drug substance* can also be used to refer to a physical mixture of two or more drug substances used to produce a fixed-combination drug product.[31]

Disproportionality Analysis: Screening of Individual Case Safety Report (ICSR) databases for reporting rates which are higher than expected. For drug-ADR pairs, common measures of disproportionality are the Proportional Reporting Ratio (PRR), the Reporting Odds Ratio (ROR), The Information Component (IC), and the Empirical Bayes Geometrical Mean (EBGM). There are also disproportionality measures for drug-drug-ADR triplets, such as Omega (Ω).[32]

Epidemiology: The science concerned with the study of the factors determining and influencing the frequency and distribution of disease, injury and other health-related events and their causes in a defined human population for the purpose of establishing programs to prevent and control their development and spread.[33]

Immunogenicity: The ability of a substance to trigger an unwanted or unanticipated immune response or reaction.[34]

Immune System: A system that protects the body against foreign substances and pathogens, including virus and bacteria.[35]

Marketing Authorization Holder (MAH): The person or company in whose name the marketing authorization has been granted. This party is responsible for all aspects of the product, including quality and compliance with the conditions of marketing authorization. The authorization holder must be subject to legislation in the country that issued the marketing authorization, which normally means being physically located in the country.[36]

National Regulatory Agency (NRA): Public authority or government agency responsible for exercising autonomous authority over some area of human activity in a regulatory or supervisory capacity.[37]

Originator Product: A medicine which has been licensed by the national regulatory authorities on the basis of a full registration dossier; i.e. the approved indication(s) for use were granted on the basis of full quality, efficacy and safety data.[38]

Pharmacodynamics: Is the exploration of what the Medicinal Product does to the body.[39]

Pharmacoepidemiology: Study of the use and effects of drugs in large populations.[40]

Pharmacovigilance (PV): The science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem.[41]

Signal: Reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously. Usually more than a single report is required to generate a signal, depending upon the seriousness of the event and the quality of the information. The publication of a signal usually implies the need for some kind of review or action.[42]

Similar Biotherapeutic Product (SBP) or Biosimilar: A biotherapeutic product which is similar in terms of quality, safety and efficacy to an already licensed reference biotherapeutic product. Note: The WHO prefers to use the term SBP. [43]

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