



IFPMA

Position Paper

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IFPMA Position Paper on Pharmacovigilance Principles for Biotherapeutic Medicines

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 possible drug-related problems”. As a result, pharmacovigilance systems are widely recognized as important tools in the regulatory process for medicines, for protecting public health and as an integral component of patient healthcare. The WHO describes a national pharmacovigilance system “as an obligatory investment in the future public health of the territory.”¹

A fundamental driver for establishing a national pharmacovigilance system is based on the premise that it is not possible to completely characterize the safety profile of a new medicine prior to the marketing authorization being granted², solely through pre-authorization clinical trials. This is due to the limitations of interventional clinical trials in comparison to post marketing use, e.g. patient numbers and inclusion criteria of patients enrolled in clinical trials compared to the heterogeneous nature of patients in the post marketing setting. Consequently, post-marketing surveillance, as part of an overarching pharmacovigilance system, is an important tool that allows both the marketing authorization holder (MAH) and health authorities to continuously assess the benefit/risk balance of a medicine throughout its life-cycle. Post-marketing surveillance identifies new safety signals, which may include potentially rare, long latency and/ or serious adverse events that were not identifiable prior to marketing authorization approval.

Maintaining a robust pharmacovigilance system relies on consistent and accurate acquisition, integration and analysis of adverse event data. Without a strong foundation, important safety signals may not be fully identified and evaluated; this strong foundation is needed for all medicines, whether they are small molecules, biotherapeutics, including biosimilars, or vaccines.

With respect to biotherapeutic medicines³, product characteristics and variability require robust monitoring and review at the batch level to ensure patient safety. Differences may occur both between the reference biotherapeutic medicines and biosimilars and between individual batches of the same medicinal product. Therefore adverse events need to be tracked in relation to both the individual biotherapeutic medicine and individual batches.⁴ In response to expected challenges of associating specific adverse events with specific batches of biotherapeutic medicines, national regulatory authorities

¹ World Health Organization. (2006) The Safety of Medicines in Public Health Programmes: Pharmacovigilance an essential tool.

² Brian L. Strom MD, MPH, (2017) Pharmacoepidemiology, Fourth Edition, Chapter 7, John Wiley & Sons, Inc.

³ Giezen T.J., M.T. A. (2008) Safety-Related Regulatory Actions for Biologicals Approved in the United States and the European Union.

⁴ Grampp G. Felix T. (2015) Pharmacovigilance Considerations for Biosimilars in the USA. BioDrugs



(NRAs), including those in the European Union (EU) and United States (US), have expressed the importance of obtaining from the reporter of the adverse event the batch/lot number of the biotherapeutic medicine concerned.^{5, 6, 7} These pharmacovigilance requirements should not be conflated with regulatory efforts to strengthen the supply chain and protect against substandard and falsified products. To provide some context for what this means in practical terms, we outline both the EU and US approach to implementing product-specific pharmacovigilance.

In the EU, European Commission Directive 2010/84/EU⁴ and guidance on good pharmacovigilance practice from the European Medicines Agency (EMA) and Heads of Medicines Agency (HMA), sets the expectation that member states shall 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 biotherapeutic 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; and that the product name and batch number of an administered biotherapeutic medicine should be recorded by the healthcare professional and be provided to the patient.⁵

In the US, the FDA's final naming guidance for all biologic products states that it will implement a distinguishable nonproprietary name designated for each originator biotherapeutic medicine, related biotherapeutic medicine, and biosimilar product which will include a combination of the core name and a distinguishing suffix that is devoid of meaning and composed of four lowercase letters. The FDA's rationale for this naming approach is two-fold:

"(1) (to) encourage routine use of designated suffixes in ordering, prescribing, dispensing, recordkeeping, and pharmacovigilance practices and (2) (to) avoid inaccurate perceptions of the safety and effectiveness of biotherapeutic medicines based on their licensure pathway".⁶ US State laws have also been passed that aim to maintain traceability of a product dispensed by a pharmacist when it is different from the product prescribed.⁸

Taking into account these additional requirements for pharmacovigilance systems for biotherapeutic medicines, IFPMA has outlined several points for all stakeholders to consider regarding the relationship between pharmacovigilance, its systems and these medicinal products.

Points for Consideration:

- In a multisource environment, a shared non-proprietary name alone does not allow for product specific traceability. Unique product identification of all biotherapeutic medicines, including biosimilars, otherwise known as Similar Biologic Products (SBPs), may significantly improve clear traceability, safe prescription and dispensing of medicines to patients, and enable

⁵ European Medicines Agency (2010): Directive 2010/84/EU of the European Parliament and of the Council of 15 December 2010 amending, existing pharmacovigilance laws contained in Directive 2001/83/EC. EMA.

⁶ European Medicines Agency (2017): Guideline on good pharmacovigilance practices (GVP) Product-or Population-Specific Considerations II. Biological medicinal products.

⁷ US Food and Drug Administration Guidance for Industry (2017): Nonproprietary Naming of Biological Products.

⁸ NCSL (2018): State Laws and Legislation Related to Biologic Medications and Substitution of Biosimilars.



accurate reporting and analysis of adverse event data. A distinguishable nonproprietary naming approach, such as the WHO Biological Qualifier proposal, may be one method to address this.⁹

- All medicines have the potential to cause adverse events. Biotherapeutic medicines have unique product characteristics, due to their biological nature and complex structure, and are much more sensitive to manufacturing and handling conditions. The adverse event / benefit risk profile presented by biotherapeutic medicines can have distinctive elements, e.g. immune responses (immunogenicity)³, including potential long-term effects on immuno-surveillance and carcinogenicity, among others. These adverse events which can impact clinical effectiveness and/or safety may be too rare or appear in time durations longer than interventional clinical studies, to be detectable during the pre-authorization setting.
- Healthcare providers should be encouraged to clearly document the batch/lot number and manufacturer's name as this will facilitate accurate attribution of events and analysis of data. It is important to ensure that healthcare providers are aware of the need to use the unique product identification, such as brand name, manufacturer name, distinguishable non-proprietary name (if present) rather than using a shared non-proprietary name when reporting adverse events. This unique product identification would allow MAHs and NRAs to clearly investigate reports from the market and allow investigation of specific batches of biotherapeutic medicine with respect to the reaction, to determine whether a change or a new safety signal (including loss of efficacy) has been identified for the class, e.g., TNF- α blockade; at the product level, e.g. all anti-TNF- α biotherapeutic medicines; or at the individual product or product batch level, originator and biosimilar, to allow regulatory agencies, MAHs, prescribers and patients to act as appropriate.
- Healthcare providers should be made aware of the necessity to use unique product identification such as brand names or distinguishable nonproprietary names (if present) when prescribing biotherapeutic medicines as well as for adverse event reporting. 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 inadvertent automatic substitution, potential changes in the biotherapeutic's clinical performance and subsequent inaccurate attribution of adverse events as the prescribing physician may not be aware of which medicine the patient received.
- National pharmacovigilance systems implemented by the NRA should be easy to use to allow reporting by both patients and healthcare providers and well-structured to facilitate the meaningful analysis of adverse event data on biotherapeutic medicines. MAHs, NRAs and medical researchers should be able to perform analyses, as appropriate, at the product class, e.g. epoetin, insulin, and individual product level, i.e. separated by manufacturer or MAH for each individual biotherapeutic medicine.

⁹ WHO (2015): Biological Qualifier: An INN Proposal Programme on International Nonproprietary Names (INN)



- Scientific opinion and regulatory experience to date does not indicate that greater or lesser rigor is required in the collection of pharmacovigilance data across biotherapeutics product types, e.g. for biosimilars when compared with –reference biotherapeutic medicines. All biotechnology manufacturers, whether they are a reference biotherapeutic medicine or SBP producer, must adhere to the regulatory requirements of the authorizing concerned regulatory agency with respect to manufacturing and pharmacovigilance; these may be based on harmonized approaches e.g., those of ICH, or CIOMS), but there is potential for divergence across regulatory authorities in how these harmonized guidelines are adopted and implemented. Common to all regulatory authority requirements is the protection of patient safety and maintenance of the quality of pharmacovigilance practices. Therefore, each MAH of each biotherapeutic medicine must have an established pharmacovigilance system to ensure comprehensive monitoring of the product and each regulatory authority authorizing a biotherapeutic medicine should have in place a national system of pharmacovigilance monitoring the safety of the product, including loss of efficacy as an adverse event.
- The ability to uniquely identify biotherapeutic medicines is even more urgent in those territories where a formal assessment of biosimilarity is not required either due to lack of guidance¹⁰ at the time of registration¹¹, or where comparability to a reference product may not have been appropriately demonstrated. These typically enter the market using the same non-proprietary name as the reference biotherapeutic medicine without appropriate scientific justification and comprehensive evidence of structural, preclinical and clinical similarity.¹²
- Proposed systems to maintain the integrity of the supply chain and guard against substandard and falsified products e.g. the barcode system in the European Union (EU) are not designed for pharmacovigilance and do not replace the need for unique product identification mentioned in previous points.

For more information

1. WHO Pharmacovigilance

http://www.who.int/medicines/areas/quality_safety/safety_efficacy/pharmvigi/en/index.html

2. WHO Collaborating Centre for International Drug Monitoring <http://www.who-umc.org/>

3. International Society of Pharmacovigilance <http://www.isoponline.org/>

¹⁰ WHO (2015): Regulatory assessment of approved rDNA-derived biotherapeutics: Addendum to Annex 4 of WHO TRS, No. 987. Annex

¹¹ A non-comparable biotherapeutic product describes those biotherapeutic medicinal products that are intended to “copy” another biotherapeutic product but that have not been directly compared and analyzed against an already licensed reference biotherapeutic product (RBP); and have not been approved via a regulatory pathway that is in alignment with World Health Organization Similar Biotherapeutic Product guidelines that ensure quality, safety, and efficacy. They may be incorrectly referred to as ‘biosimilars’ or ‘similar biotherapeutic products’.

¹² IFPMA (2014): Non-comparable Biotherapeutic Products