IFPMA

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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 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]

One driver for establishing a national pharmacovigilance system is that it is not possible to completely characterize the safety profile of a new medicine through clinical investigation[1] before the marketing authorization is first granted. Consequently, post-marketing surveillance (as part of a pharmacovigilance system) is an important tool that allows health authorities to continue to assess benefit/risk throughout the life-cycle of a medicine and potentially detect rare and serious adverse events that were not detectable before marketing authorization. Pharmacovigilance can also identify new safety signals related to product quality and/or changes in use and prescription patterns.

Maintaining a robust pharmacovigilance system relies on consistent and accurate acquisition, integration and analysis of adverse event data.[2] Without such a strong foundation important safety signals may not be fully identified and evaluated. While this need for a strong foundation is common to all medicines, it is particularly important for biotherapeutic medicines[3] where due to distinct product characteristics adverse events need to be tracked in relation to the individual biotherapeutic product. Regulators in the European Union (EU) are already putting additional mechanisms in place[4] to strengthen pharmacovigilance monitoring to ensure accurate attribution of adverse events and the United States Food and Drug Administration has made similar suggestions in their draft similar biotherapeutic product (SBP) guidance[5] issued in February 2012.

To provide some context for what this means in practical terms, the European Commission Directive 2010/84/EU[4] has defined the following expectation for EU member states. According to Article 102 (e) Member States shall:

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

[1] Note: before marketing authorization, medicines are typically studied between 5-10 years and in hundreds to thousands of clinical trial participants.

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adverse reaction report, with due regard to the name of the medicinal product, in accordance with Article 1(20), and the batch number;"

With this need for a strengthened pharmacovigilance system for biotherapeutic medicines, IFPMA has outlined several points below for consideration regarding the relationship between pharmacovigilance, its systems and biotherapeutic medicines.

General Points for Consideration:

- All medicines have the potential to cause adverse events. Biotherapeutic medicines have unique product characteristics, due to their biological nature and complex structure that require individual product adverse event tracking, such as those related to unwanted immune responses (immunogenicity)[3] , events which may be too rare to be detectable during clinical trials prior to the marketing authorization and which can lead to adverse events or even decreased efficacy.

- Pharmacovigilance systems 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. Health authorities, agencies and medical researchers should be able to perform analyses at both the product class (e.g. epoetin) and individual product level (i.e. separated by manufacturer or marketing authorization holder) for each individual biotherapeutic product.

- Currently, there is no scientific basis to conclude that greater or lesser rigor in the collection of pharmacovigilance data for Similar Biotherapeutic Products (SBPs) is required when compared with originator products.[6] Ensuring that all biotechnology manufacturers, independent of whether they are originator or SBP producers, adhere to global standards for manufacturing and pharmacovigilance (WHO, ICH, CIOMS,)[7] will protect patient safety and maintain the quality of existing pharmacovigilance practices. Therefore, each marketing authorization holder of each biological product must have an established pharmacovigilance system to ensure comprehensive monitoring of the product.

- Each biotherapeutic medicine including SBPs should be required to have a distinct name that clearly distinguishes it from other biotherapeutic medicines. This will ensure clear identification, safe prescription and dispensing of medicines to patients, and enable accurate reporting and analysis of adverse event data (i.e. improve traceability).

- Even though the clinical effect of certain products may be similar, healthcare providers should be educated on the necessity for using these distinct 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 adverse events as the prescribing physician may not be aware of which medicine the patient received.

- It is very important that adverse events are properly assigned to the correct medicine suspected of having caused the reaction, especially because of the potential risk of adverse immunogenic reactions for biotherapeutic products in the post-approval period, some which may only occur many months after the initiation of the treatment. To ensure that any adverse events reported are assigned to the correct biotherapeutic medicine, it is important that healthcare providers be educated on the need to use the distinct name rather than rely solely on the non-proprietary name when reporting adverse events.

- Healthcare providers should also 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.

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/

References

1. The Safety of Medicines in Public Health Programmes: Pharmacovigilance an essential tool, 2006.
2. The WHO has created guidelines for pharmacovigilance systems that can be found at the following web site:

   http://www.who.int/medicines/areas/quality_safety/safety_efficacy/PharmacovigilanceB.pdf
3. Giezen *et al*. Safety-Related Regulatory Actions for Biologicals Approved in the United States and the European Union. JAMA, 2008; 300(16): 1887.
4. 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
5. Guidance for Industry. Scientific considerations in demonstrating biosimilarity to a reference product (February 2012); section VIII
6. Similar biotherapeutic product (SBP)/Biosimilar: A biotherapeutic product which is similar in terms of quality, safety and efficacy to an already licensed reference biotherapeutic product. *Note:* The World Health Organization (WHO) prefers to use the term SBP. (WHO guidelines on evaluation of SBPs, Oct.2009.)

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. (WHO guidelines on evaluation of SBPs, Oct.2009.)

7. World Health Organization 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/

About IFPMA

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IFPMA manages global initiatives including: IFPMA Developing World Health Partnerships studies and identifies trends for the research-based pharmaceutical industry's long-term partnership programs to improve health in developing countries, IFPMA Code of Practice sets standards for ethical promotion of medicines, IFPMA Clinical Trials Portal helps patients and health professionals find out about ongoing clinical trials and trial results.