



# Pharmacovigilance and Risk Management for Biosimilars: Unique Challenges and Possible Solutions

Biological medicines (biologics) have made substantial contributions to the treatment of many chronic and serious diseases such as cancers, chronic inflammatory diseases and some rare genetic disorders and are expected to provide significant therapeutic benefits to many patients who would otherwise have had limited treatment options.

However, biologics are enormously expensive, making them largely unavailable to a majority of patients who need them but cannot afford them. Aging populations and a growing burden of chronic diseases including cancers have put tremendous pressure on healthcare systems all over the world, increasing demand for cost-effective medicines. Pharmaceutical generic drugs have been available for many decades, in part serving this need. However, biologics (other than blood products and vaccines) are relatively recent in origin and are well beyond the reach of many patients due to their high price. In addition to the unique biological source material and complex manufacturing and purification processes required to produce them on commercial scale, many biologics are still under patent – one of the factors contributing to their high price.

The monopoly of innovator biologics will end soon. It is estimated that around two dozen biological products with global sales of more than US\$67 billion will go out of patent this year.<sup>1</sup> The list includes drugs like Herceptin® (Trastuzumab), Avastin® (bevacizumab) and HUMIRA® (adalimumab). End-of-patent exclusivity and advances in biotechnology facilitating their manufacture have opened up huge opportunities for follow-on biologics, or biosimilars, to enter the market and serve the needs of patients all over the world in a cost-effective manner. This is clearly evident in Europe, which started approving biosimilars in 2006.

IMS Health forecasts that the global biologics market will reach \$200 billion in 2016-2017 and \$250 billion this year. Biosimilars and non-original biologics will represent 4 – 10% of that \$250 billion market total this year (equating to \$10 – 25 billion).<sup>2</sup> Although the cost differential for biologics is not as dramatic as typically seen with a generic, the price of a biosimilar is on average between 10% and 35% lower than the respective reference product.<sup>3</sup> Growth in biosimilars will therefore certainly drive down healthcare costs and generate significant savings for healthcare systems.

Development of biosimilars or follow-on biologics is therefore an undeniable reality. However, unlike a generic chemical drug, a follow-on biologic is similar but not exactly identical to the reference innovator product, and this poses unique challenges in its development and regulatory approval process. Biological drugs are large therapeutic proteins and are enormously complex in structure. Their manufacture requires complicated biological production and purification processes in highly controlled environmental conditions and under strict quality controls. A slight difference in the biological starting material (such as a genetically modified cell line or organism) or a minor change in a step in the manufacturing/purification process can have a significant impact on the quality and purity of the product, and may result in a product with appreciably different characteristics and a variable efficacy and safety profile as compared to the reference innovator product.<sup>4</sup> The comparability standards for approval of biosimilars are distinct from those for pharmaceutical products.<sup>5</sup>

Regulatory norms and standards are still evolving for biosimilars. The European Medicines Agency (EMA) has been a pioneer in establishing the framework for biosimilars and approved the first wave of biosimilar products for the European market. Around 20 biosimilars, spanning five product classes, are currently approved by the EMA. Other regions are following suit, slowly yet surely. In March 2015, the U.S. FDA approved ZARXIO® (filgrastim-sndz), the first biosimilar product approved in the U.S., opening the door for more such products in the near future. Biosimilars have their own unique challenges, namely the data required to be generated for their approval and establishing their equivalence to the reference product, and ensuring their safety. This paper focuses on pharmacovigilance (PV) and risk management for biosimilars, the issues and challenges faced in monitoring their safety and possible solutions.

## **Pharmacovigilance Considerations for Biosimilars**

Post-approval PV is extremely important for biosimilars due to the nature of conditions they treat and the fact that fewer patients are exposed to a biologic during developmental clinical trials.

In the case of biosimilars, even fewer patients are exposed to it as the number/size of studies required for approval of a biosimilar is much less compared to the innovator. Therefore, chances of detecting a safety profile different from the innovator are slim. This is compounded by the fact that patients receiving these drugs are often seriously ill and receiving multiple medications, making safety data from trial patients more complex and difficult to evaluate. In addition, because biologics are complex proteins that may stay longer in the body and undergo modifications through biological pathways, safety concerns for these molecules are likely to manifest at variable periods which may be outside of the time course of controlled clinical trials.<sup>6</sup> Hence, the safety profile of a biologic is not fully elucidated when it is first approved.

Since a biosimilar drug is not identical to the reference innovator product, the efficacy and safety data generated for the latter cannot be directly and completely transferred to the biosimilar. Both its efficacy in various therapeutic indications and its safety profile in diverse risk populations may be different from that of the innovator. Hence, compared to a chemical generic, there is a bigger need for strict post-marketing product vigilance and additional post-approval studies in the case of biosimilar products. To detect possible differences between the reference and biosimilar product, it is crucially important to compare the frequency and severity of known side effects of the reference product with that of the biosimilar. Due to the limited size of studies required for approval, any difference in the safety profile or new side effects not yet observed with the reference product can only become apparent through the painstaking collection and evaluation of post-marketing data once the product is on the market.

The discussion is still open on what (if any) post-marketing monitoring and safety-related requirements (such as special requirements related to safety reporting, post-marketing studies, or on the information that must appear in labeling for physicians or patients) should be imposed on biosimilar applicants. Both the U.S. FDA and the EMA focus on post-marketing safety programs based on the current PV laws applicable in the region.<sup>7</sup> The new EU PV legislation that came into effect in July 2012 recognizes that biosimilars and other biological medicinal products present distinct safety challenges. Automatic substitution is not allowed for biological medicines, including biosimilars. Product leaflets for biologics must include warnings that the product information only applies to a specifically named biological medicinal product and the warning must state that “changing to any other biological medicinal product should be authorized by the prescribing physician who should document the name of the product prescribed for PV reasons.” Pharmacists must record the name and batch number of any dispensed medicinal product. The legislation also recognizes the risks associated with biosimilars and puts these products in the same class as new substances. This means that manufacturers must include a ‘black symbol’ in the product information.<sup>8</sup>

## **Challenges and Solutions in Safety Monitoring and Risk Management for Biosimilars**

### **Traceability and Accurate Product Identification**

#### **1. Naming**

Despite the fact that a biosimilar and the reference drug can show similar efficacy, the biosimilar may exhibit a different safety profile in terms of nature, seriousness or incidence of adverse reactions. Therefore, when an adverse event (AE) is reported in relation to the use of a biologic/biosimilar product, there is a need to clearly identify the product associated with the AE. This is possible only if detailed and accurate information, including the correct brand name, manufacturer’s name and even the batch number of the product is collected when the AE is received in the PV system. This would be immensely

challenging if biosimilars are named like the chemical generics i.e., with their international non-proprietary names (INNs) alone, without any distinct identifier to pinpoint to the origin of the product.

Different regions of the world have different naming conventions for biosimilars. The World Health Organization (WHO) requires that biosimilars use INNs that are the same as those of the reference products since the products are essentially similar. Biosimilars in Europe have also generally used the non-proprietary names of their reference products. Australia's Therapeutic Goods Administration (TGA) issued a guidance in July 2013 that requires the non-proprietary name of a biosimilar be composed of the reference product non-proprietary name plus a biosimilar identifier consisting of the prefix 'sim' and a three-letter unique identifier code. Japan also requires that biosimilars of complex protein products bear unique non-proprietary names. Such non-unified naming conventions can cause tremendous confusion in product identification.

In order to curb the different naming systems in existence today, the WHO, through a draft policy released in July 2014, proposed a biological qualifier (BQ) system that would involve tagging a biosimilar with a random alphabetic code to represent a biologically active substance manufactured at a specific site. This would complement the use of INN. In view of this, in January 2015, Australia's TGA announced that their previously proposed naming policy (stated above) will be kept in abeyance until a final decision is reached on naming, and in the interim, biosimilar products would use TRADENAME+ Australian Business Name (ABN).

The FDA draft guidance released in August 2015<sup>9</sup> proposes that reference products and biosimilars have non-proprietary names (also called proper names) that share a core drug substance name and, in order to better identify each product, an FDA-designated suffix that is unique for each product. This suffix would be composed of four lowercase letters and not carry any meaning. For example, the non-proprietary name of a reference product could be replicamab-cznm, and a biosimilar to that product could be replicamab-hixf. The proposed naming convention seeks to address two main issues:

- ▶ To help prevent inadvertent substitution (which could lead to medication errors) of biological products that are not determined to be interchangeable by the FDA; and
- ▶ To support safety monitoring of all biological products after they are on the market, by making it easier to accurately track usage of biological products in all settings of care, such as outpatient, hospital and pharmacy settings

## 2. Substitution

Unlike a chemical generic, a biosimilar cannot always be substituted for the reference innovator product unless the products are deemed as interchangeable by the regulators. Not aware of the unique problems with biological drugs, such substitution might happen at the pharmacy level. Reporting of AEs related to the product by the healthcare provider (HCP) or a consumer may include either the name of the original innovator brand prescribed by the physician or only the INN without mentioning the manufacturer name, increasing the confusion. Moreover, the prescriber would not know what product was dispensed, only what he/she prescribed, and given that follow-up with the HCP is almost always attempted when an AE is reported, it adds to the potential for discrepancy. It is also important to report the batch/lot number of the product in question, as batch-to-batch variations in the manufacturing process or conditions, or a change in manufacturing site, may result in new safety issues. This was clearly demonstrated when cases of pure red cell aplasia (PRCA) were reported after the formulation of Eprex<sup>®</sup> (epoetin alfa) was changed.<sup>10</sup>

Accurate identification of the product involved is therefore extremely important. Possible regulatory solutions to this problem are currently being deliberated and include assigning distinct proprietary names to biosimilar products from different manufacturers, adding the manufacturing company's name to the INN to identify who the product belongs to, making products non-substitutable or non-interchangeable at the dispensing level, and only allowing substitution by the prescribing physician after appropriate evaluation of benefit to risk of such substitution. The Australian regulatory authority TGA requires the following details when submitting AE reports for biosimilar products:

- ▶ The trade name
- ▶ The entire non-proprietary name (including any biosimilar identifier)
- ▶ The Australian Registration (AustR) number
- ▶ The batch number and expiry date
- ▶ The dosage form and presentation

Additional steps being evaluated by some innovator companies include designing distinct packaging, adding quick response (QR) or bar codes to each pack of the drug or similar unique solutions that may, however, add to the cost of production and hence the price. At the dispensing level, it would be worthwhile capturing details of the product being dispensed to each patient in an electronic database, for future reference. At the level of sponsor companies or service providers, this problem can be addressed by taking down details of the product including the brand name, manufacturing company's name, batch/lot number or even requesting the reporter to send a photograph of the package in question when an adverse reaction in relation to its use is reported. Product identification will be greatly facilitated by having a database of biological and biosimilar products available in a particular country/region. Additionally, PV teams must develop and practice specific scripts to take down all details about the product in the initial or follow-up call/communication when an AE report is received for a biological product.

### **Adverse Events Related to Immunogenicity**

One of the most important safety concerns relating to biopharmaceuticals (including biosimilars) is their potential for immunogenicity, which is because biologics are complex proteins and have the capacity to trigger an immune response against themselves in the body. This response may be humoral (neutralizing or non-neutralizing antibodies) or cellular, and may manifest in a variety of ways such as anaphylaxis, hypersensitivity and infusion reactions, cross-reactivity to endogenous proteins, altered pharmacokinetics (PK) of the molecule, or loss or lack of clinical efficacy.<sup>10</sup> In the case of biosimilars, the nature and severity of immunogenicity reactions could vary from those seen with the reference innovator product, and immunogenicity data from the reference innovator product cannot be directly extrapolated to the biosimilar.

An additional hurdle in establishing immunogenicity of a biologic product could be the variable and often long "at-risk window" – the period from administration of the product to appearance of the risk. This is because biologics are complex proteins and they may persist in the body over a long time. They may even get modified due to the host's biologic processes forming different protein molecules capable of their own immunogenic potential. This may result in a longer, variable period between the intake of a biologic product and when the reaction is seen, making causality assessment difficult. This fact must be kept in mind by the safety assessment teams while evaluating potential cases of immunogenicity in association with a biologic product.

Full characterization of immunogenicity reactions for a biosimilar may not be established during approval studies. Evaluation of immunogenicity requires long-term studies as well as continued post-marketing

surveillance in the form of diligent collection and assessment of individual case safety reports and, if possible, cohort event monitoring by way of establishing a patient registry. All potential immunologic reactions reported in association with a biosimilar product should be thoroughly evaluated and medically assessed in order to identify and characterize risks that may be different from the reference product. Review of individual cases as well as aggregate data on a frequent basis is needed in order to fully understand immunogenic potential of a biosimilar product.

### **Information in the Label**

Labeling is critical to safe and effective use of a medicinal product. When an adverse reaction to the drug is encountered, information in the label is used to decide whether a specific AE/safety issue is already identified as a risk or could be a new potential safety issue. As a biosimilar drug is not identical to its reference innovator product, safety data of the innovator product cannot be implicitly and completely applied to the biosimilar, though most class-related safety issues would be common to both. This makes it imperative that all adverse reactions reported with the use of a biosimilar product should be carefully evaluated in order to identify potential risks.

The general principle of labeling for biosimilars, based on the 2012 EMA guideline, is that the label for a biosimilar medicine has to be consistent with that of the reference medicinal product for the common information applicable to the biosimilar product.<sup>11</sup> However, the unique nature of a biosimilar requires a labeling approach that combines information on both the reference product and the specific biosimilar product, linking each piece of information to the source product. Moreover, there must be “adequate mechanisms” to differentiate between AEs associated with the biosimilar product and referenced product, including the ability to identify AEs that have not been previously associated with the reference product. This is in contrast with the situation for chemical generics where there is an acceptance that the profile of each is the same and label changes for generics are driven by changes to the innovator label.

The EU PV legislation mandates that all new medicinal products (small molecule and biological medicines, including biosimilars) approved after January 1, 2011 are subject to closer monitoring for safety. These products under additional monitoring are identified by a black inverted triangle displayed in their labeling [package leaflet and summary of medicinal product characteristics (SmPC)]. Additional monitoring lasts for five years or until certain conditions have been fulfilled. This would ensure that all biological products including biosimilars are under special watch to identify potential safety issues early, facilitating proactive risk management.

### **Risk Management Plan (RMP)**

Data from pre-authorization clinical studies are normally not enough to identify all potential differences between the biosimilar and its reference product. Therefore, clinical safety of similar biological medicinal products must be monitored closely on an ongoing basis during the post-approval phase, including continued risk-benefit assessment. EMA requires that the biosimilar applicant must submit a risk management plan (EU-RMP) and PV program with its application. The information must include a description of the potential safety issues associated with the similar biological medicinal product that may be as a result of differences in the manufacturing process from the reference biologic. Thus, the safety specifications in the RMP of a biosimilar would include both identified and potential risks of the reference product, as well as risks identified from studies on the specific biosimilar product, making the safety profile as complete as possible. The RMP for the biosimilar should focus on PV measures built to identify, evaluate and mitigate these risks; identify immunogenicity risks; and implement special post-marketing surveillance. The RMP thus needs to be customized to that specific product rather than being a copy of the RMP for the reference biologic.

## Requirement for Post-Approval Studies

Both EU and U.S. guidelines require extensive analytical studies to show comparability of the biosimilar to the reference innovator product. Clinical comparability is established by a stepwise procedure with PK and pharmacodynamics (PD) studies followed by clinical efficacy and safety trials. PD parameters are selected on the basis of their relevance to demonstrate therapeutic efficacy of the product. If there are several potential indications, the most sensitive disease model to detect differences is chosen in a homogeneous patient population.<sup>12</sup> Also, usually it is recommended to evaluate safety data within the scope of combined safety and efficacy trials, hence, the size of the safety population evaluated may be small. Consequently, there is need for additional post-approval studies to establish efficacy in indications not studied during the approval process and long-term safety studies to establish immunogenic potential and other safety issues that may be different from the reference product or are rarer or appear after long-term use. In Europe, immunogenicity data for the reference product cannot be directly transferred to the biosimilar and additional studies to characterize immunogenicity are required. Marketing authorization for a biosimilar may be granted subject to the condition to conduct post-authorization safety study (PASS) and/or drug utilization study (DUS).

## Cohort Event Monitoring

While spontaneous safety reporting is a passive way to gather safety data, and is severely limited by under-reporting and inadequate details, patient/disease registries (for cohort event monitoring) are a tool for active safety surveillance. Registries allow better definition of prescriber and patient profiles, indications the product is being used for, doses prescribed, AEs, clinical outcomes and any compliance issues related to the product use. Registries are extremely useful for detecting safety issues early in post-marketing user population. New AEs including rare events or latent onset events can be detected sooner than through spontaneous reporting system and better qualification of known AEs can be done in the cohort being followed. Since the safety profile of a biosimilar is not yet fully known, such cohort event monitoring is extremely useful to identify new safety issues, especially those different from the reference biological, so that effective risk management can be undertaken sooner.

## Conclusions

End-of-patent exclusivity and advances in biotechnology facilitating their manufacture have created significant opportunities for follow-on biologics, or biosimilars, to enter the market and serve the needs of patients all over the world in a cost-effective manner. However, PV and risk management for biosimilars presents a number of unique and significant challenges. Routine PV processes may need to be adapted to address these issues. Some measures that could be adopted include:

- ▶ Maintaining a repository of information on biological products available in the region (brand names, packaging including color, etc.) which will help in correct identification of the product involved when an adverse reaction is reported in the PV system
- ▶ Developing special scripts that would allow for the collection of detailed information on the product associated with the adverse reaction in the initial or follow-up communication
- ▶ Ensuring careful medical evaluation of all suspected immunogenicity reports with understanding of “at risk window”
- ▶ Implementing frequent aggregate review of safety data and comparison with the safety profile of the reference product to understand the differences in risk profile
- ▶ Designing a RMP with additional measures to detect/evaluate yet unknown safety issues, including immunogenicity and long-term or rare events
- ▶ Setting up special product/patient registries for cohort event monitoring

- ▶ Conducting adequately powered post-approval efficacy and safety studies in all indications and target populations
- ▶ Having a product label with efficacy and safety information related to both the reference product and biosimilar identified by source (innovator or company data).

Biosimilars have been widely available and safely used in Europe since 2006. Despite rigorous safety monitoring and tracking, no significant safety issues have been identified as yet. This provides a measure of assurance that safety and risk management for biosimilars can be effectively managed by carefully and diligently following regulatory guidelines and good PV practices.

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