Ensuring Effective Safety & Risk Management for Biosimilars

The use of biopharmaceuticals has significantly increased in recent decades. Biosimilars are new biopharmaceuticals that are similar but not identical to the innovator product. Characteristics of biopharmaceuticals are closely related to the manufacturing process, which implies that the products cannot be exactly duplicated. Minuscule differences in the products structure and manufacturing process can result in different clinical outcome. This raises concerns over the safety, efficacy and even pharmacovigilance of biosimilars. This article will focus on pharmacovigilance and risk management for biosimilars, the issues and challenges faced in monitoring their safety and possible solutions.

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

**Pharmacovigilance:** Post-approval pharmacovigilance is of vital importance for a biosimilar as fewer patients are exposed to it during development, since the number/size of studies required for approval of a biosimilar is much smaller compared to that for the innovator. Furthermore, because biologics are complex proteins which may stay longer in the body safety concerns may only become apparent outside of the timeframe of controlled clinical trials.4

Since a biosimilar drug is not a replica of the reference innovator product, the efficacy and safety data generated for the latter cannot be directly and completely transferred to the biosimilar. Hence, compared to a chemical generic there is a bigger need for strict post-marketing product vigilance for a biosimilar in order to correlate its safety profile with that of the reference product, and to detect additional safety issues.

**Accurate Product Identification:** Despite the fact that a biosimilar and the reference drug can show similar efficacy, the biosimilar can 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 biosimilar product, there is a need to clearly identify the product associated with the AE. Product naming therefore becomes an important issue for biologics/biosimilars. While the EU follows the International Non-proprietary Names (INN), the US Food and Drug Administration (FDA) is still in the process of developing its policy on biosimilar naming. Possible regulatory solutions to aid product identification currently being deliberated include assigning distinct proprietary names to biosimilar products from different manufacturers, adding manufacturing company’s name and specific codes to the product labels, and making biological products non-substitutable or non-interchangeable at the dispensing level. On the part of PV teams, collecting detailed and accurate information on the product
involved (including the correct brand name, manufacturer’s name and even the batch number) when an AE is received is of paramount importance.

**Adverse Events Related to Immunogenicity:**

An important safety concern relating to biosimilars is their potential for immunogenicity. Biologics are complex proteins and have the capacity to trigger an immune response that may be humoral or cellular, and could become apparent in a variety of ways such as anaphylaxis, hypersensitivity and infusion reactions, cross-reactivity to endogenous proteins, altered pharmacokinetics of the molecule, or loss or lack of clinical efficacy. In the case of biosimilars, the nature and severity of immunogenicity reactions could vary from those seen with the reference innovator product. An additional hurdle in establishing immunogenicity of a biologic product could be the variable and often long “at-risk window.” Biologics may persist in the body over a long time, resulting in a long, variable period between the intake and appearance of the reaction, making causality assessment difficult. Full characterisation of immunogenicity profile of a biosimilar may not be established at the time of approval. Hence, long term studies as well as continued post-marketing surveillance become crucial for risk management.

**Information on the Label:** Labelling is critical to the 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 adverse event/safety issue is already identified as a risk or could be a new, potential safety issue.

The general principle of labelling 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. However, the unique nature of a biosimilar requires a labelling 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 adverse events associated with the biosimilar product and referenced product, including the ability to identify adverse events that have not been previously associated with the reference product.

**Risk Management Plan (RMP):** Data from pre-authorisation clinical studies are 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 pharmacovigilance programme 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.

**Requirement for Post-Approval Studies:** Both EU and the US 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 Pharmacokinetics (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. 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 which may be different from the reference product.

**Cohort Event Monitoring:** While spontaneous safety reporting is a passive way to gather safety data, it is limited by under-reporting and inadequate details. Patient/disease registries are a tool for active safety surveillance and are extremely useful for detecting safety issues early in post-marketing user population. New adverse events 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.

**Summary**

End of patent exclusivity and advances in biotechnology have unleashed opportunities for follow-on biosimilars to enter the market and serve the needs of patients globally in a cost-effective manner. However, pharmacovigilance (PV) and risk management for biosimilars presents a number of challenges. Routine PV processes may need to be adapted to address these issues and some possible measures include: maintaining a repository of information on biological products available, developing special scripts that would allow for the collection of detailed information on the product.
associated with the AE, careful medical evaluation of all suspected immunogenicity reports, understanding of “at risk window”, implementing frequent aggregate review of safety data and comparison with the safety profile of the reference product, designing an RMP with additional measures to detect/evaluate yet unknown safety issues, 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 and having a product label with efficacy and safety information related to both the reference product and biosimilar identified by source.

A number of biosimilars have been available in Europe for more than a decade now and despite rigorous safety monitoring and tracking, no significant safety issues have been identified with these products. 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 pharmacovigilance practices. ■

References

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