It is now widely acknowledged that the new frontier of biomedical research lies in biologics, which hold the potential to yield, over time, effective treatments for conditions or diseases hitherto considered incurable or untreatable. The fight against cancer has already received a significant boost from developments in biologics and it is expected that they will provide significant therapeutic benefit to a large number of patients with malignancies, chronic inflammatory diseases and autoimmune disorders. However, on the scale of medical development, biologics are a fairly recent innovation and the majority of them are still under patent. Moreover, their unique source materials and complex manufacturing and purification processes make them extremely expensive, thereby limiting their availability to ordinary patients, and in public healthcare systems.

Nevertheless, the global outlook for biologics is positive and it is estimated that approximately two-dozen biological products with global sales of more than $67 billion will come off patent by 2020. Advances in biotechnology and the end of patent exclusivity have resulted in burgeoning opportunities for cost-effective follow-on biologics, commonly known as ‘biosimilars’ to enter the market. IMS Health forecasts that the global biologics market will expand to $250 billion annually by 2020, with biosimilars and non-original biologics commanding 4-10% of that market, as seen in Figure 1.2
While this market share does not seem very significant, it must be borne in mind that biosimilars are priced, on average, 10% to 35% lower than their respective reference innovator products. Therefore, even a moderate growth of the biosimilars market will drive down healthcare costs and generate significant savings for healthcare systems.

Unlike generic chemical drugs, biosimilars are similar but not identical to their respective reference innovator products: this fact introduces multiple challenges in the development, safety monitoring, and regulatory approval process of biosimilars. This article focuses on pharmacovigilance (PV) and risk management aspects of biosimilars, the issues and challenges faced in monitoring their safety, and possible solutions to overcome these challenges.

**BIOSIMILARS – CHALLENGES IN SAFETY AND RISK MANAGEMENT**

Post-approval PV is critical for all biologics, and particularly so for biosimilars. Firstly, patients taking biologics are often seriously ill and receive multiple medications concurrently, making safety data from patients complex and difficult to evaluate. Furthermore, because biologics are proteins that may persist in the body and undergo modifications through biological pathways, safety concerns may only become apparent outside the timeframes of controlled clinical trials. Since the number/size of studies required for regulatory approval of a biosimilar is much smaller than that required for the original biologic, relatively fewer patients are exposed to the biosimilar during development, so the likelihood of detecting a safety profile different from the innovator is low, this in turn makes post-approval safety monitoring even more important.

A biosimilar drug is not identical to the reference innovator product, hence the efficacy and safety data generated for the latter cannot be directly and completely applied 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 product. Thus, compared to a chemical generic drug, there is a greater need for strict post-marketing product vigilance for a biosimilar in order to construct a more relevant safety profile and to detect additional safety issues.

The following are some important considerations for the safety and risk management of biosimilars:

**TRACEABILITY AND ACCURACY IN PRODUCT IDENTIFICATION**

While a biosimilar and its reference drug can show similar efficacy, the biosimilar can exhibit a different safety profile with respect to the nature, seriousness, or incidence of reported adverse events (AEs). Therefore, when an AE is reported in relation to the use of a biologic, there is a need to clearly identify the specific product associated with the AE. It follows, therefore, that product naming is an important consideration in the case of biologics/biosimilars for traceability or accurate product identification.

While the EU follows the International Non-proprietary Names (INN) standard, the U.S. Food and Drug Administration (FDA) is still in the process of finalizing its policy on biosimilar nomenclature. In order to curb the different naming systems in existence today, the World Health Organization (WHO)-INN, 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.

Other solutions proposed include: assigning distinctive proprietary names to biosimilar products from different manufacturers, or adding the manufacturer’s name and specific codes to INN. These solutions are still being deliberated. For PV teams, collecting detailed and accurate information about the prod-
ADVERSE EVENTS ASSOCIATED WITH IMMUNOGENICITY

The potential for immunogenicity represents an important safety concern with all biologics, including biosimilars. Biologics being complex proteins possess the capacity to trigger an immune response that may be humoral or cellular and that could become apparent in a variety of ways, such as through anaphylaxis, hypersensitivity and infusion reactions, cross-reactivity to endogenous proteins, altered pharmacokinetics of the molecule, or loss or lack of clinical efficacy. With respect to biosimilars in particular, the nature and severity of immunogenic reactions may differ from those observed for the reference innovator product and immunogenicity data from the reference product cannot be directly extrapolated to the biosimilar.

An additional hurdle in establishing the immunogenicity of biologics is the variable and sometimes long “at-risk window.” Since biologics may persist in the body over a longer timeframe, this could result in a lengthy and variable period between intake of the drug and appearance of the reaction, thereby rendering causality assessment difficult. Given the relatively small number/size of clinical trials required for regulatory approval of biosimilars, full characterization of the immunogenic profile of a biosimilar may not be established at the time of regulatory approval. Hence, long-term studies as well as continued post-marketing surveillance of biosimilars are critical for effective risk management.

LABELING

Accurate and complete labeling is critical to the safe and effective use of a medicinal product. When an adverse reaction to the drug is encountered, information from the label is used to decide whether a specific AE/safety issue has been previously identified as a risk or whether it may be a new potential safety issue. Biosimilars being non-identical to their reference products, the safety data of the innovator product cannot be implicitly and completely applied to the biosimilar. This makes it imperative that all adverse reactions reported with the use of a biosimilar should be evaluated carefully in order to identify potential risks.

The 2012 EMA guidelines outline the broad principle of biosimilar labeling: The label for a biosimilar product must be consistent with that of the reference innovator product for the common information applicable to the biosimilar product. However, the unique nature of each biosimilar requires a labeling approach that combines data on the reference innovator product with data specific to the biosimilar product due to differences in their source materials, manufacturing processes and impurities.

RISK MANAGEMENT PLAN (RMP)

As has been noted previously in this article, data from pre-authorization clinical studies of biosimilars are insufficient for identifying all potential differences between a biosimilar and its reference innovator product. Therefore, the clinical safety of biosimilars must be monitored closely on an ongoing basis during the post-approval phase, including through continued risk-benefit assessment. The EMA requires that a biosimilar applicant submit a risk management plan (EU-RMP) and PV plan with the application. The information to be furnished includes a description of the potential safety issues associated with the biosimilar that may arise from differences in the manufacturing process with the reference innovator product. Thus, the safety specifications in the RMP of a biosimilar include the identified and potential risks of the reference innovator product as well as risks identified from studies on the specific biosimilar product.

REQUIREMENT FOR POST-APPROVAL STUDIES

Both EU and US guidelines require that extensive analytical studies be undertaken to demonstrate the comparability of the biosimilar to the reference innovator product. Clinical comparability is established stepwise, with pharmacokinetics (PK) and pharmacodynamics (PD) studies followed by clinical efficacy and safety trials. PD parameters are selected on the basis of their relevance with a view to demonstrating the therapeutic efficacy of the product.

If there are several potential indications, the most sensitive disease model to detect differences in a homogeneous patient population is chosen. It is recommended that safety data be evaluated 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 the immunogenic potential and other safety issues that may be different from those of the reference product.

COHORT EVENT MONITORING/PATIENT REGISTRIES

Spontaneous safety reporting is a passive way to gather safety data and is limited by underreporting and inadequate details. On the other hand, patient/disease registries are an effective tool to facilitate active safety surveillance. Registries allow for 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.

Consequently, registries are extremely useful for detecting safety issues early in a post-marketing user population. New AEs, including rare events or latent onset events, can be detected sooner than through a spontaneous reporting system; additionally, better qualification of known AEs can be undertaken in the cohort being monitored. Post-marketing safety of biologics, including biosimilars can be effectively monitored through patient registries.

MEETING THE CHALLENGES

Traditional PV processes, which have evolved primarily to serve the needs of the chemical drugs market, may not incorporate sufficient provisions to meet the particular requirements for biosimilars. Consequently, when adding biosimilars to their portfolio, organizations may consider consulting with an external agency that can evaluate the current PV workflow, identify gaps, and implement new processes. Further, some PV operations for biosimilars may be outsourced to partners who have the expertise and staff to meet the additional challenges that biosimilars present.
SUMMARY

Advances in biotechnology and the end of patent exclusivity have ensured that a world of opportunities has now opened up for biosimilars to enter the market and serve the needs of patients globally and in a cost-effective manner. However, PV and risk management for biosimilars present a number of significant challenges that arise from their unique characteristics as biologics as well as from their differences with the reference innovator products. Consequently, routine PV processes may need to be adapted to address these issues.

The solutions proposed include: (i) maintenance of a data repository on all available biologics products, (ii) development of special scripts that would allow for the collection of detailed information on the product associated with the AE, (iii) careful medical evaluation of all suspected immunogenicity reports, (iv) understanding of the “at risk window”, (v) implementation of frequent aggregate reviews of safety data and comparison with the safety profile of the reference product, (vi) creation of an RMP with additional measures to detect/evaluate potential and unknown safety issues, (vii) setup of special product/patient registries for cohort event monitoring, (viii) undertaking adequately powered post-approval efficacy and safety studies in all indications and target populations, and (ix) product labeling with efficacy and safety information related to both the reference product and biosimilar identified by source. To meet the myriad regulatory challenges posed by biosimilars, organizations may consider appointing an outsourcing partner that specializes in these processes and capabilities. CP

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