BEMS Reports. 2017; 3(2): 67-69
A Multifaceted Peer Reviewed Journal in the field of Biology, Medicine, Engineering and Science
www.bemsreports.org | www.phcog.net

Mini Review

Preclinical Safety Considerations for Biosimilars

Koppal Suryanarayana Rao

INTRODUCTION

It is now a foregone conclusion 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. On the scale of medical development, biologics are a fairly recent innovation and the majority of them are still under patent protection. 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.

Unlike generic chemical drugs, biosimilars are similar but not identical to their respective reference innovator products. Even minor changes to the original manufacturing process may result in alterations to the secondary, tertiary, and quaternary structure of the molecule, which may have an impact on the efficacy and safety of the drug in various therapeutic indications and its safety profile in diverse risk populations may be different from that of the innovator product. The assessment of toxicity and safety of monoclonal antibodies (mAbs) becomes more challenging because of the higher complexity and size of these products, giving rise to higher variability. The manufacturing of biosimilar mAbs can lead to differences in glycosylation pattern, resulting in a high level of micro-heterogeneity. In addition, mAbs often have a complex mode of action as they comprise multifunctional molecules with biological properties involving both their Fab and Fc fragments. Many challenges are associated with the approval process of biosimilar mAbs.

Thus, the demonstration of high similarity to the reference product regarding quality, safety and efficacy is necessary to detect additional safety issues and possible solutions to overcome these challenges. The latter introduces multiple challenges in the development, safety monitoring, and regulatory approval process of biosimilars. This write up focuses on issues and challenges faced in monitoring their preclinical safety and regulatory aspects surrounding this dilemma. No effort will be made to discuss the clinical testing aspects in this write up.

How similar?

A biosimilar is generally defined as a biological medicine developed to be similar to a biological medicine already approved for human use (the "reference" product).

Biosimilars have to demonstrate similarity with their innovator compound (predecessor), though how similar has been a moving target. The nature and complexity of the reference product have an impact on the extent of the non-clinical studies to confirm biosimilarity. The differences observed in the physico-chemical and biological analyses will guide the planning of the non-clinical studies. Other factors that need to be taken into consideration are the mode of action of the active substance (e.g. receptor(s) involved) in all the authorized indications of the reference product and pathogenic mechanisms involved in the disorders included in the therapeutic indications (e.g. mechanisms shared by various therapeutic indications) as well as the immunogenicity of the reference medicinal product.

General requirements for biosimilars

The purpose of a biosimilar development program is to support a demonstration of biosimilarity between a proposed product and a reference product, including an assessment of the effects of any observed differences between the products, but not to independently establish the safety and effectiveness of the proposed product.

Agencies generally employ a stepwise approach to demonstrating biosimilarity, which can include a comparison of the proposed product and the reference product with respect to structure, function, animal toxicity, human pharmacokinetics (PK) and pharmacodynamics (PD), clinical immunogenicity, and clinical safety and effectiveness.

The guidelines offered by the US and the EU are very generic and do not necessarily give specific list of studies per se. Both guidance give lot of room for negotiations and flexibility for a case by case assessment and testing. In addition, both regulators recommend dialogue with the agency. In principle, only a reference product licensed in the EU or the US, respectively, is accepted for any kind of testing during the approval process of a biosimilar drug. However, there is some provision, on a case by case basis, wherein an alternate source of reference product can be used.

Cite this article : Rao KS. Preclinical Safety Considerations for Biosimilars. BEMS Reports, 2017;3(2):67-9

Koppal Suryanarayana Rao
Senior Director – Strategic Business Development, Eurofins Advinus Limited, 21 and 22, Phase II, Peenya Industrial Area, Bengaluru – 560 058, Karnataka, INDIA.

Correspondence

Dr. Koppal Suryanarayana Rao,
M.V.Sc., Ph.D., DABT

Senior Director – Strategic Business Development, Eurofins Advinus Limited, 21 and 22, Phase II, Peenya Industrial Area, Bengaluru – 560 058, Karnataka, INDIA.

Email: toxrao@gmail.com

Phone: +91-733-783-0074

DOI : 10.5530/bems.3.2.8

Article Available online
http://www.bemsreports.org

An application submitted to the agency must contain, among other things, information demonstrating that "the biological product is biosimilar to a reference product" based upon data derived from:

Analytical studies that demonstrate that the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components;

In vitro biological assays such as,

(1) Binding to target(s) (e.g. receptors, antigens, enzymes) known to be involved in the pharmaco-toxicological effects and/or pharmacokinetics of the reference product.

(2) Signal transduction and functional activity/viability of cells known to be of relevance for the pharmaco-toxicological effects of the reference product.

(3) Comparative assessment of the mAb's effector function (Antibody Dependent Cell-mediated Cytotoxicity (ADCC) and Complement Dependent Cytotoxicity (CDC) as well as antigen binding studies and a target neutralization assay;

(4) Animal studies (including comparative PK and assessment of toxicity); and

(5) A clinical study or studies (including the assessment of immunogenicity and pharmacokinetics or pharmacodynamics) that are sufficient to demonstrate safety, purity, and potency in one or more appropriate conditions of use for which the reference product is licensed and intended to be used and for which licensure is sought for the biological product.

(6) Agencies generally recommend that sponsors use a stepwise approach to develop the evidence needed to demonstrate biosimilarity. Agency intends to consider the totality of the evidence provided by a sponsor when the Agency evaluates the sponsor's demonstration of biosimilarity, consistent with a longstanding Agency approach to evaluating scientific evidence.

Preclinical Safety Studies Needed for a Biosimilar - non-clinical testing strategies

Animal toxicity data are considered useful when, based on the results of extensive structural and functional characterization, uncertainties remain about the safety of the proposed product that need to be addressed before initiation of clinical studies in humans.

If comparative structural and functional data using the proposed product provide strong support for analytical similarity to a reference product, then limited animal toxicity data may be sufficient to support initial clinical use of the proposed product. Such a study may be non-sacrificial and include endpoints that measure in-life parameters, PD, and PK.

If the structural and functional data are limited in scope or there are concerns about the proposed product quality, a general toxicology study may be needed that includes full animal pathology, histopathology, PD, PK, and immunogenicity assessments. When animal toxicology studies are conducted, it will be useful to perform a comparative study with the proposed product and the reference product.

Animal toxicity studies are generally not useful if there is no animal species that can provide pharmacologically relevant data for the product. Some agencies which require routine rat and/or rabbit toxicity studies, which do not have specific receptors, are wasting resources as these studies have no relevance to human safety.

In the EU and the US, *in vivo* studies are usually required in relevant species based on state-of-the-art technology. Since most mAbs have relevant receptors in primates, if at all any animal studies are needed, based on residual lack of similarity in the biosimilar with the innovator product, one must consider a repeat dose toxicity study in monkeys. One four-week in non-human primate (NHP) with TK and local tolerance is appropriate to conduct. The latter has added value in some cases which is basis of regulatory approval. In such repeat dose toxicity studies, it is mandatory to include assessment of immunogenicity, or at least collect blood for immunologic (ADA) assessment which can be done. Additionally, differences observed in animal immunogenicity assessments may reflect potential structural or functional differences between the two products not captured by other analytical methods.

Furthermore, consistent with the recommendations of EMA, non-clinical safety pharmacology, reproductive and developmental toxicity as well as carcinogenicity studies are not warranted in the US when the proposed product and reference product have been demonstrated to be highly similar by extensive structural and functional characterization. In August 2012, FDA proposed a risk-based approach stating that animal repeated-dose toxicity studies may not be required, and may only be useful if safety uncertainties remain before first-in-man studies.

Adverse Events Associated with Immunogenicity

The potential to trigger immunogenic responses in humans 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 so immunogenicity data from the reference product cannot be directly extrapolated to the biosimilar. Therefore, the immunogenicity issue has become a focus area in their development and approval. In the case of monoclonal antibodies (mAbs), these may cause safety issues, alter activity or have an impact on both parameters. For example, antibodies neutralizing endogenous erythropoietin (EPO) can result in a rare condition known as antibody-mediated pure red cell aplasia (PRCA), which was observed inter alia after a manufacturing change initially considered to be minor to the originator product Eprex® (a synthetic erythropoietin). Regarding biosimilar products currently approved by European Medical Agency (EMA), there are still some concerns in the long-term evaluation of these products, particularly the limited experience at the time of approval in terms of safety and their potential to trigger immunogenicity.

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 immunogenicity profile of a biosimilar may not be established at the time of regulatory approval.

Both EMA and FDA agree that animal immunogenicity studies do not predict potential immunogenic responses to protein products in humans. However, if differences in manufacturing, e.g. the presence of impurities or excipients, between the proposed product and the reference product result in altered immunogenicity, measurement of anti-protein antibody responses in animals may provide useful information relevant to patient safety. Overall, a step-wise testing approach before entering the clinical phase is required in both the US and the EU.

Regulatory Status of Biosimilars

US and Europe: While still considered 'new,' biosimilars aren't a new approach to therapies, but are more accurately described as still being a nascent industry. This is because the regulatory track record is still immature—only a handful of approvals by the top companies producing these drugs and working with regulatory authorities on stabilizing the requirements. EMA was the first competent authority to issue guidelines for biosimilar approval in 2005. In February 2012, FDA issued draft guidance documents regarding the approval of biosimilars. As of this time 5 biosimilars have been approved in US. This is interesting to compare with Europe, where to date 14 biosimilars have been approved covering only three reference products.

Japan: At the 14th Annual Biosimilars Group Conference (2016), Dr Daisaku Sato, Director, Office of Cellular and Tissue-based Products at the Pharmaceutical and Medical Devices Agency (PMDA), discussed whether repeat-dose toxicity studies are required for marketing applications for biosimilars in Japan, as follows:

A sponsor should evaluate the non-clinical safety of their biosimilar candidate prior to entering into clinical studies, in accordance with ICH S6

However, in cases where there are no concerns about non-clinical safety based on characterization studies and comparison of the physicochemical and pharmacological properties, *in vivo* toxicity studies may be not required

This approach should be evaluated on a case-by-case basis

Korea: The Korean FDA guidelines require that at least one repeat-dose study be performed in a relevant species, using state-of-the-art technology, and that, depending on route of administration of a biosimilar product, a local tolerance study may need to be performed. If comparability of the biosimilar product and reference product is verified through quality evaluation, other toxicological studies are not generally required, unless triggered by results of the repeat-dose toxicity study and/or by other known toxicological properties of the reference product.

Mexico: The Mexican guidelines provide significantly less detail than the other guidelines. However, they note that preclinical studies on animals, comparing the reference product and the biosimilar product, should be carried out in animal species relevant to the study model and must include a comparative study of the PD effect and activity relevant to the clinical application, as well as a comparative toxicology report in at least one toxicity study of repeated dosage, including toxicokinetic measurements. They also state that the study duration should allow the detection of relevant differences in toxicity and immune responses between the biosimilar and the reference product.

Brazil: At the time of the protocol of the application for registration of a biological product, the requesting company shall submit the complete reports of the non-clinical studies.

The studies shall be comparative and designed to detect significant differences between the biological product and the comparative biological product.

Article 45 – states that the applicant shall submit the reports of the following non-clinical *in-vivo* studies :

I - Pharmacodynamic studies relevant to the intended therapeutic indications; and

II - cumulative (repeated-dose) toxicity studies, including characterization of toxicity kinetics parameters, conducted in relevant species (s).

India: Indian Government Biotechnology Department guidelines allow use of at least one rodent species repeat dose toxicity study. Many companies use it as an entry point in India, which is not keeping with the Western regulated countries, since a rodent study has no safety value because of lack of receptors for the biosimilar.

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. By and large, most regulators expect stringent chemical similarity from primary to quarternary level, followed by *in vitro* and *in vivo* functionality and compared with the innovator product.

With the advent of biosimilars, the traditional preclinical program has changed to a new paradigm that integrates the concept of comparability with existing knowledge of the biopharmaceutical reference drug. Recently, the recommended preclinical program espoused by the European Medicines Agency has been modified to an abbreviated one that now emphasizes *in vitro* studies in lieu of *in vivo* for monoclonal antibody biosimilars. Likewise, the US FDA guidance on biosimilars suggests a flexible approach rather than an automatic 28-day comparative toxicology studies that have historically been conducted for worldwide marketing. Conducting repeat dose rodent toxicity studies for biosimilar has no safety value which some countries require. For now, structure and function studies will continue to be the foundation of the overall analytical assessment of biosimilarity. Traditionally, comparative animal safety assessments will have limited value in determination of biosimilarity and in an abbreviated design they may have most value in providing assurance of safety in first-in-human trials when structural attributes are not indistinguishable.

Overall, it can be seen that a range of non-clinical considerations should take place to develop a Such considerations include the relevant biological and pharmacological studies sand, for toxicology testing, the relevant species of use, study design and comparator requirements, all with the aim of showing comparability but with the avoidance of unnecessary animal use.

Cite this article : Rao KS. Preclinical Safety Considerations for Biosimilars. BEMS Reports, 2017;3(2):67-9