Handbook of Biologics & Biosimilars in Dermatology

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Concept and Development of Biosimilars

Brijesh Nair

INTRODUCTION

Biosimilars are biopharmaceuticals that have been assessed by regulatory agencies to have efficacy and safety similar to their reference products and are expected to be marketed at substantially lower prices. They are not 100% identical, but essentially the same biological substance, though there may be minor differences due to their complex nature and production methods. They have come into the limelight because of patent expiry of originator biological molecules. The new wave of biosimilars will largely consist of monoclonal antibodies, which are mainly used in the oncology and immunology setting. Biologicals have revolutionized the field of medicine and dermatology in particular, with significant impact in the management of psoriasis, psoriatic arthritis (PsA), and urticarial and immunobullous disorders. The expected benefits of biosimilars are reductions in costs and consequently better access to biotherapeutics. However, uptake of biosimilars in the market has been slower than expected, which may, at least partly, be attributed to a lack of trust in the efficacy and safety of biosimilars as well as their interchangeability with the originator product by both patients and clinicians, which needs to be addressed meticulously. The difference in philosophy of biosimilar development is the focus on detection of potential differences in efficacy rather than the demonstration of efficacy, per se. "The demonstration of comparability does not necessarily mean that the quality attributes of the pre-change and post-change product are identical, but that they are highly similar and that the existing knowledge is sufficiently predictive to ensure that any differences in quality attributes have no adverse impact upon safety or efficacy of the drug product."

As such, a biosimilar development is therefore not so much "abridged" but rather "tailored" toward a distinct scientific objective—that is, to establish biosimilarity, not to re-establish benefit for the patient. The current concept of development of biosimilar monoclonal antibodies/soluble receptor fusion proteins (mAbs/cepts) follows the principle that extensive state-of-the-art

physicochemical, analytical, and functional comparison of the molecules is complemented by comparative nonclinical and clinical data that establishes equivalent efficacy and safety in a clinical "model" indication that is most sensitive to detect any minor differences (if these exist) between biosimilar and its reference mAb also at the clinical level.[1,2]

DEFINITION: BIOSIMILARS

The European Medicines Agency (EMA) defines biosimilars as "biological medicinal products that contain a version of the active substance of an already authorized, original biological medicinal product (reference medicinal product). A biosimilar agent is similar to the reference medicinal product in terms of quality characteristics, biological activity, safety and efficacy based on a comprehensive comparability exercise."

The intention of the biosimilar development is to show similarity with the reference product, not to independently demonstrate patient benefit. The scientific principles for establishing biosimilarity are the same as those for demonstrating comparability after a change in the manufacturing process of an already licensed biological originator molecule. According to US legislation, biosimilars must utilize the same mechanism or mechanisms of action for the condition or conditions of use prescribed, recommended, or suggested in the proposed labeling and are prescribed for conditions that have been previously approved for the reference product. Furthermore, the route of administration, the dosage form, and the strength of the biosimilar should be the same as those of the reference product.[3-5]

Why is Biosimilar Development Complex?

Biologicals are derived from living cells or organisms and consist of relatively large and often highly complex molecular entities that may be difficult to fully characterize. Because of inherent variability of the biologic system and the manufacturing process, any resulting biological will display a certain degree of variability (microheterogeneity), even between different batches of the same product. Because of unavoidable differences in the manufacturing processes, a biosimilar and the respective originator product, the reference product, will not be entirely identical. However, the amino acid sequence is expected to be the same, and only small differences in the microheterogeneity pattern of the molecule may be acceptable. A very thorough comparison of the structural and functional characteristics and the product and process-related impurities of the biosimilar and the reference product is essential. Any differences found will need to be explained and justified with regard to the potential impact on the clinical performance of the biosimilar. Hence, the data requirements for demonstration of biosimilarity will usually be more extensive than for demonstration of comparability of a given biological before and after manufacturing changes by the same manufacturer. Data requirements for the development and

licensing of biosimilars are considerably greater than for small chemically synthesized generic molecules. For a generic, physicochemical identification and demonstration of a similar pharmacokinetic profile (bioequivalence) to the originator product are usually sufficient to conclude on therapeutic equivalence. In contrast, a biosimilar needs to be developed based on a more extensive head-to-head comparison with the reference product, to ensure close resemblance in physicochemical and biologic characteristics, safety, and efficacy. The focus of biosimilar development is not to establish patient's benefit per se—this has already been done for the originator product—but to convincingly demonstrate high similarity to the reference product as basis for relying, in part, on its efficacy and safety experience.

Clinicians need to be aware that clinical data are not the only cornerstone of a biosimilar development to be relied on. Extensive characterization and comparison of the physicochemical properties and biologic activity of the biosimilar and the originator product play a fundamental role in this, and close similarity in these aspects is a prerequisite for any reduction in the amount of nonclinical and clinical data requirements. Clinical data provide complementary information. The biosimilar development program is scientifically tailored using up-to-date analytical tools and sensitive test models to best detect even small potential product-related differences between the biosimilar and the reference product.[6-11]

PRECLINICAL ANALYTICAL ASSESSMENT

Preclinical analytical assessments are used to determine similarity to an originator biologic and are critical for regulatory approval of biosimilars. Approximately 40 different analytical methods are utilized to assess 100 different drug attributes. The International Psoriasis Council suggested guidelines for standardization of preclinical assessments of emerging biosimilars through the development of a biosimilar index. Companies in the business of making biosimilars are not in possession of the original cell line utilized for the originator compound, and thus their biologic, derived from a new cell line, is not identical to the original product. Instead of relying on any one key piece of data, the weight of all the analytical assessments is considered when determining whether the biosimilar is "similar" to the originator compound, the choice of the cell line, the culture media, the culture temperature, and the purification processes can all be altered, with each change potentially affecting the quality of the end product. The primary amino acid composition of a biosimilar medication is precisely bioengineered, but other features of biologics such as three-dimensional protein folding, glycosylation, charge, and presence of impurities are more variable during the manufacturing process. These particular features of a biologically produced product may affect both the antigen binding and immunogenicity of a given drug, and thus may affect both drug efficacy and

safety in clinical use. Evaluating post-translational modifications via mass spectrometry, including testing for glycosylation, acetylation, sulfation, phosphorylation, glycation, and charge, is essential in the characterization of biologics and biosimilars. Testing for drug product stability (e.g., shelf life and alterations with temperature) and product devices (e.g., autoinjectors, prefilled syringes) are also needed in order to determine similarity between the biosimilar product and originator biological product.[12-14]

Biosimilar index is an algorithm where each comparison is weighted with regard to its criticality, and where variability for each assay/test, (e.g., <10% or 1 SD) is standardized. Using this index, biosimilars would be rated and scored regarding their preclinical analytical similarity to the originator biologic.[15]

SOME TERMINOLOGIES DEFINED

- *Biomimics*: These are versions of mAbs or fusion proteins available in countries where regulation is less strict. Biomimics are also known as "biocopies," "intended copies," or "nonregulated biologics." Kikuzubam was a rituximab biomimic that demonstrated adverse events different from originator molecule of rituximab, and hence regulatory authorities had to revoke the approval, thus demonstrating the complexity of the biomimic explosion. It also needs to be stated that different adverse effect profile of a biomimic raises questions on its biosimilarity.
- *Reference product (alternative terms—"originator" or "innovator" product)*: The initial biopharmaceutical that has been approved by regulatory agencies for specific indications; preclinical and clinical data regarding the reference product provides the basis for comparison of a biosimilar agent in the approval process.
- *Biosimilar (alternative terms—"similar biotherapeutic product," "subsequent entry biologic," "follow-on biologic," and "biocomparables")*: A mAb or fusion protein that has undergone a complete development process based on comparability to preclinical and clinical data of the reference product, with sufficient bioequivalence to meet regulatory approval.
- *Interchangeability*:[16-19] Interchangeability is the concept that a biosimilar drug and its parent biologic compound are so similar that a patient could be switched from one originator drug to another biosimilar drug and back during chronic therapeutic use, perhaps an indefinite number of times, without any untoward clinical side effects occurring due to this interchange of products. This designation allows a biosimilar agent to be substituted for its reference product by the pharmacist without prescriber input. Unlike small-molecule drugs, a biopharmaceutical that is repeatedly interchanged with a similar biological agent might elicit immunogenicity that could compromise the efficacy and safety of both the medications. Thus, the prevalent American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) consensus

is that frequent switching between the original protein product and the biosimilar agent should be avoided, as even subtle differences, such as impurities introduced during manufacturing, can trigger an immune response to biosimilar agents.

- *Switch*: Therapeutic transition from a reference product to a biosimilar agent or vice versa based on prescriber decision. A "switch" study demonstrating no loss of efficacy or no increase in risk would support the transition from biological to other.
- *Substitution*: Interchange of a biosimilar agent with its reference product by someone other than the prescribing health professional. If a biosimilar agent is determined to be "interchangeable" with its reference product, a pharmacist would be allowed to substitute a prescribed biological therapy for a biosimilar agent without involving the prescribing physician.[20,21]

METHODOLOGY OF PROVING BIOSIMILARITY

For approval, a comprehensive dossier of analytical, preclinical, pharmacokinetic, pharmacodynamics, and clinical data that demonstrates comparable efficacy and safety of the biosimilar and its off-patent reference biopharmaceutical is required. The EMA has prescribed certain steps that are mandatory for approval of a biosimilar. This process is depicted in **Table 1**.

TABLE 1: Steps for approval of biosimilar.

Stages	Steps
Preclinical stage	
In vitro studies	• Assessing binding to targets • Assess signal transduction and functional activity/viability
Determine if in vivo studies are needed	Necessary only if factors of concern are identified, for example, new post-translational modification structures
In vivo studies	Focus of study depends on the need for additional information.
Phase 1	
Pharmacokinetic/ Pharmacodynamics studies	• Single dose crossover or parallel group designs preferred • Pharmacodynamic markers selected on the basis of their clinical relevance • Affinity is a key determinant of the PK and PD profile of mAbs and soluble receptors • Close reproduction of conformational structure for biosimilar mAbs and cepts is needed to ensure comparable biological effect
Phase 3	
Safety and efficacy studies	• No clinically significant difference in efficacy to reference product • Compare severity and frequency of adverse events, in particular for immunogenicity/safety

(cepts: soluble receptor constructs; mAbs: monoclonal antibodies; PD: pharmacodynamics; PK: pharmacokinetics)

IMMUNOGENICITY

It is important to understand the complexity of production of both biological reference product and biosimilar, which precludes exact replication. Earlier batches of reference product have also changed due to the process changes and hence the current version of a biological reference product is not identical to the earlier batches of the same product. This underlines the need for rigorous pharmacological equivalence and biocomparability studies (for clinical comparison) in the approval process of a biological/biosimilar.

Immunogenicity may be influenced by patient-, disease-, or product-related factors. Patient- and disease-related factors are already known from the experience gained with the originator product and therefore do not need to be reinvestigated for the biosimilar. The focus of the evaluation is thus on potential product-related factors, such as structural or impurities/contaminants, most of which are readily detected by state-of-the-art analytical methods. Differences in immunogenicity can also be due to extraneous factors such as impurities in the manufacturing process of the prefilled syringes. This demonstrates the complexity of biosimilarity confirmation process.

In order to gain full insight into the long-term outcomes, particularly the immunogenicity profile of biosimilars, it is recommended that comparative clinical data should be collected for >1 year especially for antitumor necrosis factor (anti-TNF) therapies. Immunogenicity data beyond 1 year lacks scientific rationale and would raise the bar for biosimilars above that expected for innovator drugs, with obvious negative consequences for the affordability of these products.[22-26]

PHARMACOVIGILANCE

Pharmacovigilance, embedded in postmarketing surveillance, is of critical importance for biosimilars. As the abbreviated clinical development program of biosimilar agents is less able to identify small safety risks (compared with the development of reference products), appropriate pharmacovigilance measures need to be implemented after approval is granted. The means of pharmacovigilance are company-initiated risk management plans, postmarketing research, and surveillance of existing databases (registries) created to monitor patients receiving biologic agents.

The pharmacoequivalence and bioequivalence of the biosimilar to reference product intuitively suggests similarity in safety profile from product-related and patient-population-related perspectives. However, variability in immunogenicity due to batch-to-batch variability is a cause for concern. Thus, the safety of biosimilars needs to be actively and comprehensively followed up on an ongoing basis. Adverse event reports, if any, should include, in addition to the International Nonproprietary Name (INN), other indicators, such as brand name, manufacturer's name, lot number, and country of origin of the batch used.[27,28]

Nomenclature

To avoid confusion between biosimilar agents and their reference products during pharmacovigilance, specific nomenclature is necessary to distinguish each biosimilar from its reference drug and from each other. It has been suggested that a Greek letter or a combination of several letters could be appended to the end of the INN of each biopharmaceutical. Alternatively, a "biologic qualifier" (BQ) [a four-digit code proposed by the World Health Organization (WHO)] could be used to distinguish reference products and biosimilars from one another. Overall, the general agreement is that use of the INN alone is insufficient to differentiate biosimilars, and that traceability of each biosimilar needs to be secured. However, even though an internationally standardized system of nomenclature for biosimilars is urgently needed, this system has not yet been established, making postmarketing surveillance, risk evaluation, and management strategies for biosimilars more difficult.[29-31]

Extrapolation

Extrapolation is defined as the ability to utilize clinical study data for one disease to gain agency approval for another disease not explicitly studied in clinical trials. Extrapolation is the foundation of the biosimilar regulatory framework and is here defined as granting regulatory approval for indications of the reference medicine that are not specifically studied during the clinical development of the biosimilar medicine. The United States Food and Drug Administration (US FDA) issued guidance stating that data from a clinical trial of a biosimilar agent conducted in one disease could be used to support approval for additional indications for which the reference product has already been licensed. To obtain approval for any additional indication, the licensed biosimilar must follow the traditional regulatory pathway for biopharmaceuticals. The FDA mandates two randomized, placebo-controlled clinical trials (conducted in patients with the disease for which the indication is being sought) that demonstrate both efficacy and safety of the biological agent in that disease state. Thus, if a biosimilar agent was not approved initially for all indications for which the reference biopharmaceutical is licensed, the biosimilar manufacturer must conduct clinical trials in each additional individual disease state to support a biological license application for each separate indication. Similarly, if the reference biopharmaceutical is approved for an additional indication after its biosimilar has already been licensed, extrapolation of indications no longer applies; the manufacturer of the licensed biosimilar must conduct new clinical trials in this new indication to get approval. Thus, extrapolation of indication requires convincing scientific justification, which should address the mechanism of action, toxicities, and immunogenicity in each indication of use.[32-38]

For mAb, extrapolation is more complex as their mechanism of action may depend on multiple sites of the molecule. Often, no direct pharmacodynamic

marker exists for their activity, which means that clinical studies are designed around (insensitive) clinical end points, which makes it particularly challenging to study these products. How the different structure–activity relationships of antibodies contribute to efficacy and safety in the different indications is often not fully understood.[39,40]

Regulatory Issues

CT-P13 (an infliximab biosimilar) was the first mAb biosimilar to be approved, but not all national regulatory agencies granted extrapolation to all infliximab indications. Infliximab biosimilar (Remsima) had been approved in a total of 47 countries as of May 2014, and marketing applications were pending in an additional 23 countries. Thus, as of May 2015, CT-P13 has been approved for use in approximately 70 countries worldwide. Agencies allowed extrapolation of indications for CT-P13 to six additional diseases for which the reference infliximab is approved but in which CT-P13 was not studied, namely PsA, psoriasis, adult and juvenile Crohn disease, and adult and juvenile ulcerative colitis. This decision established a regulatory precedent for the extrapolation of indications for a therapeutic monoclonal antibody based on results of one successful phase III trial in a sensitive population [in rheumatoid arthritis (RA)] and on additional pharmacokinetic, efficacy, safety, and immunogenicity data acquired in a phase I trial of patients with a different disease [ankylosing spondylitis (AS)]. Extrapolation of indications for biosimilars is possible, but concerns have been raised regarding the potential efficacy and safety of a biosimilar in diseases for which it has not been studied. It is opined that the outcome of a biosimilarity exercise should be binary: you either are, or you are not biosimilar to a given reference product. Selective approval for extrapolation to indications is at odds with this concept. Allowing products on the market that do not have the same authorized indications will create considerable confusion about the concept of biosimilarity. The success of biosimilars will depend on how they will be able to be interchanged with the reference product and other biosimilars in clinical practice. If multiple biosimilars are allowed in the market with different approved uses, this will create a complex situation that will add hurdles for the successful practitioner uptake of biosimilars.[41-44]

INDIAN SCENARIO FOR BIOSIMILARS

There has been burgeoning interest in biosimilars in Indian dermatology scenario. Biosimilars of infliximab, etanercept, rituximab, and adalimumab have been launched. The permissive nature of regulation in India has resulted in proliferation of intended copies without published biocomparability research supporting their use. The possibility of revoking an approval on recognition of inefficacy or adverse events is a definite possibility in the current scenario. Indian guidelines allow a biosimilar product to be

TABLE 2: Biosimilars currently approved for use in India.		
Product	**Brand name/manufacturer**	**Biosimilarity status**
Adalimumab	Exemptia (Zydus)	Biosimilarity proven
	Adalirel (Reliance), Adfrar P (Torrent)	Intended copies/biomimics
Etanercept	Etacept (Cipla), Intacept (Intas)	Intended copies/biomimics
Rituximab	Reditux (Dr Reddy's), Rituxirel (Reliance), Mabtas RA (Intas)	Intended copies/biomimics
Infliximab	Infimab (Sun/Epirus/Reliance)	Biocomparability studies with switching carried out in rheumatoid arthritis. Similar study in psoriasis planned
Omalizumab	Omalirel, Emzumab	Intended copies

authorized if the reference product is licensed and widely marketed for at least 4 years in a country with a well-established regulatory framework, although not marketed in India (e.g., Humira).[45] The biosimilars currently approved for use in India are depicted in **Table 2**.

ZRC-3197, developed and marketed by Zydus Cadila (India) in India as exemptia to treat RA, juvenile inflammatory arthritis, PsA, and AS, is described as a "fingerprint match" of the reference adalimumab (Humira, Abbvie Inc, USA) "in terms of safety, purity and potency." The primary and secondary structures of ZRC-3197 and reference adalimumab are identical, and no differences were detected in aggregation or in the profile of low-molecular-weight fragments between these two biopharmaceuticals. Based on this, ZRC-3197 was approved for RA, juvenile idiopathic arthritis, AS, PsA, hidradenitis suppurativa, ulcerative colitis, and Crohn disease, but interestingly not for the treatment of psoriasis. The reason for not authorizing the product for psoriasis is not clear.[46-48]

BIOSIMILARS IN PSORIASIS

There is a paucity of biosimilar trials pertaining to psoriasis. In dermatology, direct data on psoriasis patients is missing. Most approvals are based on extrapolation. The question has been raised whether results obtained from such diverse patient populations treated with the same biologic may be compared at all. In general, psoriasis patients have been exposed to previous treatment protocols [e.g., ultraviolet (UV) therapy]. They also tend to exhibit different patient characteristics that may make them more susceptible to adverse drug reactions than other patient groups (e.g., alcohol abuse, liver toxicity). The fact that, for instance, inflammatory bowel diseases respond to infliximab and adalimumab but not to etanercept, whereas etanercept, on the other hand, is effective in psoriasis and RA also clearly underlines the

differences between the mechanistic of various autoimmune diseases. The underpowered biosimilarity studies are ill-equipped to detect safety signals. Although not all ongoing biosimilar trials may have been registered, the present situation in terms of registered trials is unsatisfactory and will leave clinicians with a high degree of uncertainty with respect to their treatment decisions. It is now up to the clinical community to start collecting data on efficacy and particularly safety with independent trials and patient registries.

Biosimilars ideally must be studied in the preferred ("most sensitive") indication to assess comparable safety and efficacy. In case of TNF inhibitors, it is psoriasis with a reliable, easily assessable clinical endpoint [Psoriasis Area and Severity Index (PASI)]. Future of biosimilar development might focus more on this "sensitivity" aspect of psoriasis.[49-51]

BIOSIMILARS FOR PSORIASIS: CLINICAL STUDIES TO DETERMINE SIMILARITY

The International Psoriasis Consortium (IPC) has defined biosimilarity in psoriasis biosimilars on a clinical level recently. The amount and the type of clinical data generated in clinical studies involving biosimilars will inherently be less than the clinical data obtained for originator biologics. Owing to the regulatory emphasis on extrapolation eventuating in cost reduction, utilizing biosimilars in practice for diseases where little or no clinical data exist is a reality that clinicians must learn to accept. The IPC has suggested psoriasis as a future model for TNF blocker testing owing to (1) high effect sizes in clinical trials, (2) lack of cointervention, (3) commonality of the disease, (4) ease of conduct of trials with an easily reproducible outcome endpoint (PASI score). IPC also suggested that a biosimilar trial should also be at least as long as the primary endpoint in the reference product's pivotal trials and be based on the same safety measures collected during these original trials. For example, TNF blocker biosimilar trials should include safety outcomes such as deaths, malignancies, opportunistic infections, reactivation of tuberculosis and hepatitis B virus, major adverse cardiac events, and injection site reactions. In many cases, to demonstrate clinical equivalence on efficacy and safety of the biosimilar and the reference biologic adequately powered, randomized, parallel group, preferably double-blinded, comparative clinical trials are needed.[52-54]

CONCLUSION

The principles of establishing biosimilarity are to demonstrate structural and functional similarity to a reference product using the most discriminatory analytical methods. These data are supported where necessary by focused clinical evaluation using conditions that are adequately sensitive to evaluate real risks that cannot be addressed solely by analytical data. Unanswered questions remain, particularly regarding extrapolation of indications,

BOX 1 Problem areas in biosimilar products.

- Consistent demonstration of pharmaceutical quality and quality assurance of the manufacturing process by biosimilar firm
- Ensuring batch to batch product consistency
- Lack of data on substitution, switching, interchangeability and subsequent adverse events/immunogenicity
- Extrapolation of data from index disease to other indications
- *Intense postmarketing surveillance for safety issues*: Pharma company, the primary stakeholder as opposed to practitioner driven registries
- Problems with inconsistent nomenclature
- Trial design complexity in demonstration of equivalence and interchangeability
- Inter-regulator variations in licensing for extrapolation based on in vitro assays
- Practitioner and patient apprehension regarding efficacy and safety of biosimilars
- Grant of license by regulator subject to a post-authorization safety surveillance commitment

switching and interchangeability, naming and traceability, and long-term safety of biosimilars. Even after licensing, biosimilars (owing to the batch to batch variability inherent to biopharmaceuticals) must be subjected to intense postmarketing surveillance and pharmacovigilance. Further studies, including postmarketing surveillance using data acquired from registries, are needed to give healthcare providers confidence to accept these biosimilar agents into their armamentarium. The tighter regulation of intended copies and biomimics must be ensured to avoid safety issues that might blight the development of genuine biosimilar agents. The appropriately regulated and rationally extrapolated biosimilar development milieu will go a long way in reducing healthcare costs in the therapy of inflammatory diseases and can augment health policy decision-making. Despite the increasing number of countries that have adopted biosimilar guidelines, there are clear differences in local requirements in terms of weight of evidence and data interpretation, labeling, and naming of biosimilars. Such divergent regulatory decisions on the biosimilarity exercise do not assist in solving the trepidation that exists at the level of healthcare professionals and patients about biosimilars. There is a need for a global harmonization exercise for deciding upon the determinants of the concept of biosimilarity and for standardizing the regulatory requirements of biosimilars **(Box 1)**.

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Handbook of Biologics & Biosimilars in Dermatology

Salient Features

- Requisites for informed and correct prescription of biologics and biosimilars in Dermatology
- Information that is required for Dermatologists in India, as well as countries with similar population demography—to prescribe biologics and biosimilars with confidence and complete information
- Material which is essential and include facts required by clinician for decision-making

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