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Review Article

An overview of biosimilars

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ABSTRACT

The paradigm of pharmacological therapy in diseases is shifting from conventional small molecule drugs to biological drugs produced by living systems. Biological drugs have extensively ramified into therapies of various conditions such as autoimmune disorders, haematological conditions, cancers and others. Biological drugs are currently the diamond mine of the pharmaceutical drug market. Due to the enormous market value, other pharmaceutical companies are keen in producing and marketing generic versions of these innovator (reference) biologic companies, once the patents start to expire. These generic versions of the biological drugs are called as biosimilars. However, biosimilars are not exactly generics of the originator biological drugs like in the case of conventional small molecule drugs. Various controversies and perplexities exist in their production, approval, marketing, and prescription. The reason for the mere existence of biosimilars or generics drugs for that matter is their reduced cost with preserved clinical effectiveness. Biosimilar drugs are subject to rigorous scrutiny by a thorough comparative evaluation with the reference biological product for marketing approval. It is also equally important for the physicians and pharmacists to have a sound body of knowledge about biosimilar drugs to optimally avail the benefits offered by them. This review highlights how biosimilar drugs differ from the conventional drugs, their development process, issues, and challenges associated with their use.

Keywords: Biosimilars, Follow-on biologics, Similar biologic medicinal products, Bio-therapeutical products

INTRODUCTION

Biological agents have greater molecular size, structural complexity, species specificity and are obtained from living systems which makes them distinct from the conventional drugs. Therapy with biological agents have transformed the treatment of various diseases like cancers, inflammatory disorders, hormone replacement etc. Biological agents constitute a rapidly flourishing sector of the pharmaceutical market, accounting for about 10% of the pharmaceutical expenditure and is expected to grow exponentialy.[1] As the patents of the original biological agents were nearing expiry, pharmaceutical companies started to produce them akin generic medicines. In contrast to conventional small molecule agents produced by chemical process, the production and analysis of biological agents are more complex and technically challenging owing to various reasons including use of a biological process system, cell lines and their inherent natural variability. These agents are called as "biosimilars" which is a biological medicinal product that contains a version of the active substance of an already authorized originator biologic. Biosimilars are also known as similar biological medicinal product, subsequent entry biologics, follow on biologics and similar biotherapeutic products.

DEFINITION OF BIOSIMILARS

FDA

The biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components and "there are no clinically meaningful differences between the biological product and the reference product in terms of safety, purity, and potency

of the product".[2] Biological product-protein except any chemically synthesized polypeptide.

EMA

A biological medicine highly similar to another biological medicine already approved in the EU (reference medicine) in terms of structure, biological activity and efficacy, safety and immunogenicity profile.[3]

Biobetters are biological agents that are designed or modified to improve their pharmacological profile and are considerably superior in terms of quality, safety and efficacy in comparison to reference biologic.[4] Example: Darbopoetin alpha with a changed glycosylation pattern with extended elimination T1/2. Intended copies are replica of an original biologic and not been evaluated using the stringent biosimilar comparability exercise established by the concerned regulatory agencies like EMA, FDA, or WHO for granting approval.[5] Thus their similarity to the original biologic product in terms of efficacy, safety, quality and clinical profile cannot be confirmed.

BIOSIMILARS VERSUS GENERIC MEDICINES

The active substance in a generic drug is identical to that of its reference product. Thus, efficacy and toxicity are also identical between them provided that the pharmacokinetics is proved similar within a predefined margin by bioequivalence studies. The molecular structure of chemical drugs or small molecules can be well established analytically with low structural complexity. Thus, development of generic drugs is relatively easier with less production costs.

In contrast to small molecules, biological agents are more complex in structure, greater molecular weight, microheterogeneity in production of proteins, post-translational modifications, 3-D conformational dependent activity etc. The molecular structure of biologicals cannot be fully established by state-of-the-art analytical techniques. Thus, the biological agents show minor variations between batches of drugs and they do not retain the principle of molecular identity. Thus, it becomes necessary for a biosimilar drug to prove comparability with the original biological drug in terms of safety and efficacy by a robust comparability exercise in addition to the complex production process.

THE BIOSIMILAR MARKET

The first biosimilar was approved was for the growth hormone somatropin in 2006 by EU.[3] Since then the biosimilar market has been expanding including the emergence of so called second generation biosimilars which comprise mAbs and fusion proteins. EU has the maximum number of approved biosimilars and vast experience of their safety and utility.[6] Biosimilars being a relatively new line of pharmaceutical product estimated to have 210 billion USD (17.5%) of the total medical spending.[7] It is estimated that the total market for biologics in cancer, across indications will reach $68 billion by 2020, as patents expire.[8] Biosimilars made up more than $150 billion in global sales in 2013, about US$ 228 billion in 2016 and are projected to reach $ 390 billion by 2020.[9,10]

THE DEMONSTRATION OF BIOSIMILARITY

FDA considers totality of the evidence provided by the sponsor for comparative assessment (head-to-head comparison) of the effects of any observed differences between the products.[2] The type and extent of testing that will be required is determined on a product specific basis. FDA recommends a 'stepwise approach' in demonstration of similarity between the proposed biosimilar product and the innovator biological product (reference).

The tests must be performed with several representative batches to understand variability of both products. Sponsors should use the finished dosage form of the proposed biosimilar product in the analysis.[11] If any change incurs the manufacture process after completion of analytical assays, additional similarity tests is expected to be performed to establish the comparability.

Step 1: Extensive structural and functional characterization of both proposed product and reference product

Generally, the tests will comprise of comparability tests on primary structure (AA sequence), higher order structure including conformation and aggregation, post-translational modifications like glycosylation and phosphorylation, variations like deamidation and oxidation and intentional changes like PEGylation sites. Functional assays include in vitro assays for biological activity, binding, signal transduction and functional activity/viability of cells and enzyme kinetics.

The studies must compare concentration-activity/binding relationship of the proposed biosimilar and the reference product at the concerned pharmacological target, encompassing a range of concentration where potential differences are most likely to be detected

Step 2: Data from animal studies

Animal studies are expected to be done if the results from animal studies can meaningfully address the remaining uncertainty and the availability of sensitive animal model. If the model allows PK and PD of the biosimilar and the reference product should be quantitatively compared, including a dose concentration response assessment. The extent of data required depends upon the level of uncertainty remaining after the previous step.

If strong similarity can be established from analytical studies, limited animal toxicity data is sufficient to support initial clinical use. Conduct of standard repeated dose toxicity studies in non-human primates is usually not

recommended and a flexible approach can be considered for safety studies. If substantial concerns exist from prior steps full toxicology study with histopathology, PK, PD, immunogenicity will be required. Generally animal models do not well predict the potential immunogenicity to protein products in human, but however it is worthwhile to obtain samples for measurement of antibody response directed against the therapeutic protein which may reflect potential structural/functional differences between the two products.

Studies regarding safety pharmacology, reproduction toxicology and carcinogenicity are not required. Studies assessing local tolerance may be required if new excipients are introduced with minimal experience with the intended clinical route of administration.

Step 3: Clinical studies

The type and extent of clinical studies depends upon the frequency and severity of safety risks associated with the innovator product, relationship between pharmacological effect and effectiveness and the level of residual uncertainty. FDA requires a comparative PK/PD study, immunogenicity assessment and additional comparative studies as needed in humans. PK and PD parameters are generally more sensitive than clinical efficacy endpoints in assessment of similarity.[12]

A comparative efficacy study may not be necessary if PK and PD results are satisfactory. Nonetheless comparative safety and immunogenicity assessments studies should still be performed. Assessment of biosimilarity doesn't require all the pivotal studies performed for the reference product in terms of safety and efficacy.

Study design

A single dose randomized crossover study is generally preferred for PK similarity assessment. Parallel design is used for products with long T1/2, increased immune response on cumulative esposure and slow PD response. For PD similarity assessments, a multiple dose design may be appropriate when PD effect is delayed. Typical study design is a equivalence with symmetric margins. The study must be of appropriate duration to allow for PD measurements, safety and immunogenicity assessments.

Study population

The study should be done in population which is most informative and sensitive. Clinical PK and PD studies should be conducted in healthy subjects if the product can be safely administered to them owing to less PK/PD variability compared to patients. Patients are to be preferred over healthy subjects if PD markers can be obtained only in patients with the relevant disease condition or due to ethical/ safety reasons. Often the study population chosen will have attributes similar with the population studied for the licensure of the reference product.

Dose selection

The dose selected must be the one which is sensitive enough to provide clinically meaningful and illustratable data. For a study in patients, the appropriate choice is the approved dose. For studies in healthy subjects, a lower dose on the steep portion of the exposure response curve has to be chosen. A spectrum of doses can be utilized in assessment of dose-response relationship if the reference product has a concentration- effect relationship that is non-linear or is highly variable.

Route of administration

The route of administration of the proposed biosimilar is often same of the reference product. If the innovator reference product has more than one route of administration, then the route chosen must be one which is most sensitive to detect differences. In utmost cases, the most sensitive route is the approved extravascular route/subcutaneous as it yields comprehension of potential PK differences over the phase of absorption and may also grant more sensitive assessment of differences in immunogenicity.

Pharmacokinetic measures

All PK parameters must be assessed. Cmax and AUC should be obtained in a relevant biological fluid. For single dose studies if IV route, AUC0-∞ is considered as the primary endpoint and for S.C route, Cmax and AUC are considered as co-primary endpoints. For multiple dose studies, AUC 0-tau is considered as primary endpoint, Ctrough SS and Cmax are considered as secondary endpoints.

Pharmacodynamic measures

The PD biosimilarity assessment should use a biomarker having a wide dynamic range over the spectrum of drug concentration, should reflect the mechanism of drug action in the concerned disease state and sensitive enough to ascertain any meaningful difference between the products. A study of multiple dose and SS is vital when a PD response is delayed and especially if the proposed therapy is intended for long term use. The comparative PD biomarker assessment is performed by determining Area under the effect curve (AUEC). If only one measure of PD is possible then the PD biomarker-drug concentration relation should be applied for assessment of similarity. The dose for PD assessments must be chosen must lie on the steep part of D-R curve.

Clinical safety

Safety data is obtained throughout the development process including the PK/PD assessments and also during the pivotal clinical efficacy study. The required comparative safety data depends upon the frequency and severity of different safety issues established for the

reference product. The specific risks anticipated for the biosimilar drug must be evaluated and submitted. Probable safety concerns resulting from a production process distinct from that of the reference product, like infusion reactions and immunogenicity must also be addressed.[12]

Immunogenicity

Biological drugs are more likely to evoke immunologic responses than small molecules because of factors like greater molecular size, subcutaneous route of administration and presence of non-human sequences. Immunogenicity can cause alteration in pharmacokinetics, can induce anaphylaxis or lead to development of neutralizing antibodies and thus can affect both safety and effectiveness of the product. The interest is to assess both the incidence and severity of immune responses in humans. In particular when the proposed biosimilar is a replacement of endogenous substance, the antibodies induced by the biosimilar product can cross react with the endogenous protein and cause enhanced suppression. The tests involve screening assays, assays for specificity of antibodies, neutralization assay and antibody charcterisation.[13]

The development of immune response against a therapeutic protein is multifactorial which comprise patient factors including genetics and immunosuppression, disease related factors, concomitant treatment, product characteristics, duration of therapy, route of administration, previous exposure etc. Thus, immunogenicity assessment has to be performed for each indication/patient population. Clinical immunogenicity studies are always needed particularly for monoclonal antibodies. At least one comparative parallel design clinical study in treatment naïve patients with sufficient follow-up (6 months to 1 year) is required pre-authorization.[11]

Quality concern

Since biosimilars are more variable and prone to change with environment conditions, the quality is of utmost importance. Thus, regulatory agencies have in place strict quality requirements which must be met for approval. Physicochemical and functional characterization must establish the quality of the finished product in terms of identity, quantity, safety, purity and potency. Product and process related impurities must be compared between various lots of proposed biosimilar and the reference product. Utmost consideration must be given to amino acid sequence, any post-translational modification, any change on exposure to reducing sugars like glycation, degradation changes (oxidation, deamination or aggregation), 3-D structure as these affect the bioactivity of the expressed protein.[14]

Any differences must be evaluated using functional assays in terms of a potential effect on protein function and stability. If the reference biological product shows multiple functional activities, (enzymatic and receptor mediated) sponsors must perform assays in order to assess the range of pertinent activities. If any change occurs in the manufacturing process after analysis of the biosimilar product, the sponsor must perform studies comparing pre and post manufacturing change products with multiple representative lots.[15]

Extrapolation across indications

If a proposed biosimilar product is proven highly similar to the reference product in a particular disease condition, the data can be extrapolated to other indications for which the reference biological product is approved, as long as supported by robust scientific evidence. To allow extrapolation the primary disease for which the biosimilarity was assessed must be the most sensitive one to discern any potential difference between the two products. The factors which must be borne while allowing extrapolation include the extent of clinical experience with the reference product, mechanism of action of the active substance in the indications, active sites of the molecule, various receptor targets involved, variability in the immunogenicity and safety across the therapeutic indications and the extent of analytical and functional characterization.

The therapeutic indications must involve same mechanism of action mediated by same receptors, similar binding characteristics, similar post-receptor binding signal transductions mechanisms and similar site & extent of target expression.[2] Additional studies may be required if the primary indication in which the biosimilarity assesses is less relevant to the safety and efficacy in other indications or the mode of action of the active substance is complex (multiple receptor interaction, more than one active site). This is especially of great concern with monoclonal antibodies and fusion proteins due to their innate complexity, heterogeneity, secondary effects and additional binding sites.

Immunogenicity data cannot be extrapolated automatically across indications and needs adequate justification as it is dependent on other factors apart from product attributes. Extrapolation is feasible only from a high-risk condition to a low-risk condition. (S.C route to I.V route and immunocompetent patient population to immunocompromised patients) and not the other way.15 Thus extrapolation of data across indications is not automatic but decided on a “case by case basis” and the sponsor must provide adequate scientific evidence both pre and post marketing.

Interchangeability

Interchangeability is exchanging the use of the biosimilar product with the originator biologic or an exchange between two biosimilars and is expected to have the same effect clinically. This can mean switching (decision made by the prescriber) or automatic substitution at pharmacy level (without knowledge of the prescriber). For EU

regions, the interchangeability is decided at the national level.

For United States, FDA decides approval whether a biosimilar is interchangeable and has set of specific guidelines. Interchangeability is granted if the sponsor provides sufficient scientific data that the proposed biosimilar product "can be expected to produce the same clinical result as the reference product in any given patient" and there is no increased risk in terms of safety and diminished efficacy with switching compared to therapy without switching. FDA requires switching studies conducted in one or more relevant conditions of use in this regard. If interchangeability is approved then the biosimilar can be substituted for the reference product without the intervention of the prescriber. The extent of evidence required pre and post marketing will depend on the complexity of the product, level of functional characterization, immunogenicity risk associated with the product.

The switching studies should involve atleast three switches alternating the products and must assess PK and PD parameters, immunogenicity and safety.[16] The switching study can be a dedicated standalone study design or can be built in as part of comparability exercise meant to demonstrate biosimilarity. It is recommended that these switching studies use patients as study population and should select a clinical condition that would allow the extrapolation to other indications. Since a proposed interchangeable product may be subject for substitution without the intervention of the prescriber, it is advised that sponsors analyse the differences in presentation and the level of human factors involved in the administration using the so called 'threshold analysis' and comparative use human factors studies. It is also advised that FDA approved reference biologics are used for the switching studies.

The threshold analyses involve labelling comparison, comparative task analysis, and physical comparison between the two products along with their respective contained closure system and/or delivery device constituent part. The intention of comparative use human factors study is to analyse any disparity in the error rates associated with the use of the two products.

Switching between the biosimilars or between a biosimilar and reference biological product should ideally be done by the prescriber, with sound knowledge about the biosimilar and after discussion and informing of the patient. It is also a good practice from prescribers to prevent substitution by other medical professionals or pharmacists by deliberately remarking on the prescription document.

BIOSIMILARS: AN ECONOMIC BOON

The prime advantage with biosimilars is the reduced cost and competition with the original innovator biologic and possibly a better immunologic profile. Thus, it is vital to be aware of the cost-effectiveness and the financial advantage gained from them.

In a report by the Drug discovery and development (IMS) institute funded by Novartis, had projected that in the absence of competition by biosimilars, the eight top-selling biologics in the United States and five European countries (Germany, France, Italy, Spain, and the United Kingdom) will have an expenditure of a total of $225 billion between 2016 and 2020. In the presence of biosimilars, the cumulative savings could range from $45 to $90 billion.[10] According to US-FDA, biosimilar savings are projected at $250 billion by the year 2024.[17]

CHALLENGES AND OTHER ISSUES WITH BIOSIMILARS

Biological drift and biological divergence

Biological agents compared to small molecules are subject to natural variability and are highly sensitive to changes in the manufacturing process. Unknown or unexpected (drift) changes in the manufacturing process system and known changes made by the sponsor in order to improve the quality, efficiency of production and convenience may result in differences clinically relevant in terms of safety, efficacy and immunogenicity. Unchecked drift and/or other changes may get cumulative over time and a considerable loss in similarity can occur between two products which were once highly similar, a phenomenon called biological divergence. This can eventually lead to modifications in the comparator used in the comparability exercise and biosimilarity may be exhibited since there is no significant change pairwise. This can be mitigated by robust control system of quality characteristics and well characterized standards.[18]

Pharmacovigilance

The comparability exercise used in the establishment of bio similarity cannot elucidate all the possible differences between the proposed biosimilar and the reference product. Inspite of exhibiting similar efficacy, the biosimilar can very well have a dissimilar safety profile in terms of severity and frequency of adverse reactions. Also, biosimilar product, the originator biologic and the patient characteristics can evolve over time. Thus, there is an increased requirement for continued assessment of risk-benefit balance of biologicals especially for second generation biosimilars. Regulatory agencies mostly require a robust post-marketing surveillance system with a risk management plan particularly for the issue of immunogenicity. This includes approaches like establishment of patient registries, prescription event monitoring, enhanced adverse event reporting etc.[19]

Nomenclature and identification

Prescribers and other health care professionals, sponsors and regulatory agencies must be able to clearly identify and

report the particular biologic drug linked with the adverse event. However, this issue of identification and traceability is not quite easy in the case of biologicals, as the drugs may evolve over time resulting in difference between manufacturers and batches of the same biological drug further complicated by interchangeability. Biosimilar drugs cannot be considered as generic drugs because of the very fact that they are not identical but rather similar to the reference product. Thus, the biosimilar drugs cannot be given the same non- proprietary name as in the case of generic small molecule drugs. It is of great importance that health care professionals, patients and regulators identify the biosimilar being used and be able to differentiate the various biosimilar available in the market.

Most regulatory agencies propose addition of a unique suffix to the INN name of the originator biological product. Example: filgrastim-sndz ZARXIO, infliximab-dyyb INFLECTRA. Other agencies use the trade name together with the INN (SANDOZ filgrastim) and greek letter suffixes.[20] According to FDA guidelines, the proprietary name of the biosimilar must be used for identification and labelling purposes.[21]

CONCLUSION

Demonstration of biosimilarity depends upon the comprehensive comparability exercise with the reference (innovator) biological product. Although biosimilars are associated with various controversies and difficultly in terms of production, quality and immunogenicity among others, the global and national market is blooming and is expected to flourish largely in the next decade. The difficulties and controversies associated with biosimilars must not hamper their advantage of low cost and availability. Considerable experience has been gained with the use of biosimilars now and the knowledge gap is on the decline with biosimilars being increasingly accepted by the medical community. The regulatory agencies worldwide are also aware of the benefit of biosimilar drugs gained by the community and observe a flexible approach with the sponsors still enforcing good standards of pharmaceutical quality, safety and efficacy. Above all it is of utmost importance that prescribers and pharmacists be well aware and informed about biosimilar drugs and their characteristics in their best utilization.

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