

Current Market and Regulatory Landscape of Biosimilars

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The introduction of biologic medications has significantly improved the outcomes of many difficult-to-treat diseases, particularly within the oncology, rheumatology, and endocrinology therapeutic areas. Many biologics, however, are highly expensive medications, which presents a significant economic burden for patients, providers, and the healthcare system overall. Biosimilars, biologic medications containing a highly similar active ingredient compared with the reference product, have the potential to reduce healthcare expenditures and improve access to potentially life-saving medications.

As biosimilars continue to advance, identifying strategies to optimally incorporate these agents into clinical practice is critical. Educating healthcare professionals (HCPs) on biosimilars and the regulatory and approval process is imperative to evidence-based decision making and patient access to optimized care.

Historical Landscape

Historically, FDA approval of generic chemical drugs was allowed by the Drug Price Competition and Patent Term Restoration Act of 1984, also known as the Hatch-Waxman Act.¹ The act is credited with lowering the cost of drugs and expanding the generic drug industry in the United States.¹ Cost savings are achieved by generics through avoiding the enormous expenses of drug research, clinical trials, and development and marketing efforts amassed by brand-name manufacturers.

The FDA Center for Drug Evaluation and Research (CDER) regulates prescription brand name and generic drugs, over-the-counter drugs, and biologics.¹ FDA approval of a generic drug requires proof of identical chemical structure and pharmacokinetic equivalence to the original product, allowing the generic manufacturer to reference the safety and efficacy data for the FDA-approved brand drug while abiding by manufacturing and reporting standards.¹ Traditional generic pharmaceuticals are not required to be evaluated in an independent clinical trial because the law permits clinical data to be extrapolated from the reference product.¹ Chemical drugs are regulated by the FDA using a new drug application (NDA) or an abbreviated new drug application (ANDA) under the Federal

ABSTRACT

The introduction of biologic therapies has improved the treatment landscape for multiple diseases, particularly in the areas of oncology, rheumatology, and endocrinology. Although they are effective, biologics are associated with increased costs that result in economic burden for healthcare professionals and patients. Biosimilars are biologic medical products that are almost an identical copy of the original product. There are differences in the regulatory requirements for the original biologic product and a biosimilar, as biosimilars gain FDA approval through an abbreviated approval pathway. The incorporation of these products into the US market will potentially result in improved patient access and decreased healthcare costs. There are barriers, such as lack of familiarity, that affect the use of biosimilars. Strategies to overcome these barriers are essential to improve the uptake of these products in the United States.

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Food, Drug, and Cosmetic Act (FDCA). This established framework provides a mechanism for the approval of generic chemical drugs.

The first biologics were developed by the industry during this time of regulatory debate and development. Human insulin (Humulin-R) was approved by the FDA in 1982, becoming the first human biologic to enter the US market. Following were human growth hormone (Protropin) in 1985, alpha interferon (Intron-A) in 1986, tissue plasminogen activator (Activase) in 1987, and erythropoietin (Epoen) in 1989.¹

Originally, certain biologics were regulated as chemical drugs under the FDCA rather than the Public Health Service Act (PHSA).¹ Congress gave the FDA authority over the marketing of insulin in 1941. During this time, biologics, such as insulin, were extracted from animals, becoming known as the “natural source.”¹ The National Institutes of Health (NIH) managed the natural source biologics with a small group being the exception, including insulin, glucagon, human growth hormone, hyaluronidase, urokinase, and several hormones that were under the authority of the FDA. The FDA lacked the authority, however, to approve biosimilars as patents for biologics expired. As a result, the US biologics market lacked the competition seen between chemical brand-name and generic drugs.¹

The NIH regulated most biological products until 1972, when the responsibility was completely transferred to the FDA. Currently, biologic agents are regulated under the PHSA (rather than the FDCA), requiring a biologics license application (BLA) to obtain licensure for marketing by the FDA.¹ Although the Hatch-Waxman Act provided a pathway of approval for generic drugs under the FDCA, the PHSA lacked a defined regulatory framework for biosimilars.¹ Manufacturers were effectively blocked from submitting follow-on applications for biologics licensed under the PHSA, and were instead limited to a niche group of said natural source biologics previously approved under the FDCA.¹

Abbreviated Approval Pathway for Biosimilars and Interchangeability

The current established legal pathway for the approval of biosimilars was achieved through the Biologics Price Competition and Innovation Act (BPCIA), signed by President Barack Obama on March 23, 2010.¹ The BPCIA was enacted as Title VII of the Affordable Care Act (ACA, P.L. 111-148). It established an abbreviated pathway for regulatory approval of biosimilars (the 351 [k] pathway), allowing the FDA discretion for marketing approval with less-extensive testing, as clinical safety and efficacy of the biologic molecule is already demonstrated by the innovator.¹ Under the act, the biosimilar sponsor is required to show that a biosimilar candidate has no clinically significant differences, aside from minor differences in clinically inactive components between it and the reference-biologic in terms of safety, purity, and potency. The sponsor is also required to demonstrate that the biosimilar is expected to

produce the same clinical effect as the reference-biologic. Thus, an approved biosimilar should not be expected to differ from the reference-biologic in safety and efficacy.

There are key differences in regulatory requirements for approval of a reference-biologic, compared with the requirements for the approval of a biosimilar. The manufacturer of the reference-biologic is required to produce analytics on the drug's composition and formula.² They must also undertake preclinical testing to identify toxicities and demonstrate therapeutic effects in an animal model. Clinical trials from phase 1 studies of the pharmacokinetics to phase 2 and phase 3 safety and efficacy studies hold the highest cost burden for these manufacturers and are necessary to demonstrate therapeutic benefit without excess toxicity for target disease.² In contrast, most of the cost burden for a biosimilar manufacturer rests on the analytics of the drug composition and formula, confirming the high similarity to the reference-biologic.² Although demonstrating similarity to the reference-biologic in terms of primary structure is straightforward, doing so for higher orders of structure (secondary, tertiary, and quaternary) is very challenging. Post-translational modifications must be identical or highly similar and variations due to oxidation and deamination warrant consideration.² Such variables, however, are inherent to all biologics and can theoretically have a significant impact on clinical safety and efficacy parameters (with both biologics and biosimilars).

Antigen binding and avidity of the biosimilar must also match that of the reference-biologic as determined by *in vitro* studies. Such studies provide data on biosimilar functions associated with antigen binding (Fab) fragment (neutralization and receptor activation) as well as functions associated with fragment crystallizable region (Fc): apoptosis, antibody-dependent, cell-mediated, and complement-dependent cytotoxicity. Of equal importance are assays on antigen binding: Fc receptor for IgG (Fcγ receptor), neonatal Fc receptor, and complement components.²

Randomized controlled trials (RCTs) for biosimilars exist to reaffirm data following the physiochemical and *in vitro* analyses.² If all data from physiochemical and *in vitro* studies imply the biosimilar and reference-biologic are equivalent, clinical efficacy is assumed. Biosimilars of this nature may require a single pharmacokinetic study to demonstrate equivalence and a single RCT to establish equivalence to the reference-biologic in clinical safety, efficacy, and immunogenicity.

Extrapolation is established in the totality of evidence presented in placebo-controlled phase 3 RCTs and functional data of the biosimilar in each condition for which licensure is sought. Such data packages may include the pharmacokinetics and biodistribution of the product in different patient populations, immunogenicity in different patient populations, and any differences in expected toxicities in each condition of use.³ Although study populations in RCTs should represent the indications sought for approval,

extrapolation between indications is normal if a common mechanism exists and equivalence is displayed in a single indication.²

Biosimilars may be further evaluated to determine interchangeability with the reference-biologic. Interchangeability is defined, under the BPCIA, as meeting a high standard of similarity to the reference-biologic and the biosimilar has no clinically meaningful difference.³ Additionally, the interchangeable product is expected to produce the same clinical result as the reference-biologic. For a product administered more than once to an individual, the risk (in terms of safety and reduced efficacy) of alternating between use of biosimilar and reference-biologic is not greater than the risk of using the reference-biologic only.³ To gain marketing approval as interchangeable, the FDA additionally requires one or more switching studies evaluating the effects of switching patients between biosimilar and reference-biologic to monitor any changes in safety events and establish interchangeability of products.³ A sponsor may seek licensure for a proposed interchangeable biosimilar in fewer than all conditions of use as the reference-biologic is licensed; it is recommended, however not required, by the FDA to seek licensure for all conditions of use held by the reference-biologic if able.³

As with all biologics, quality and purity of biosimilars are subject to changes in the manufacturing process due to modernization of equipment, changes in scaling, or improving efficiency. The International Conference on Harmonization Q5E tripartite comparability guidelines use comparability analyses to determine if a biologic medicine retains similar quality before and after changes in manufacturing processes.⁴ Such guidelines allow marketing to continue under the current product label without the need to conduct a clinical development program analyzing the product before and after manufacturing changes. Molecular changes in the product must be shown to have no impact on efficacy, safety, and immunogenicity. If analytical differences are observed and there is a questionable relation to efficacy and safety, a combination of nonclinical, clinical, and/or analytical studies may be warranted.⁵

Immunogenicity is evaluated in biosimilar clinical trials with continued monitoring post launch. Immunogenicity is complicated by many factors and is a potential cause of efficacy loss in all biologics (both reference-biologics and biosimilars). Factors affecting immunogenicity include dosing frequency, administration route, target disease, aggregates in preparation, post-translation modifications, patient genetic profile, and drug interactions. Changes in immunogenicity from reference-biologic can theoretically result in poorer clinical outcomes.⁶⁻⁸ Immunogenicity is of concern among HCPs regarding switching between reference-biologic and biosimilars (interchangeability). In the PLANETRA,⁹ PLANETAS,¹⁰ and Tanaka et al¹¹ studies, patients with rheumatoid arthritis or ankylosing spondylitis were switched between reference-infliximab and the biosimilar CT-P13, while a control group used reference-infliximab only. In the PLANETRA and Tanaka et al studies, clinical

measures of safety and efficacy were comparable between switched and nonswitched groups.^{9,11} In the PLANETAS study, there was a higher proportion of patients with more than 1 treatment-emergent adverse event (TEAE) in the switched compared with nonswitched group. The rates of TEAEs in both groups, however, were within the range and were historically reported in studies of reference-infliximab use on patients with ankylosing spondylitis and thus unlikely indicative of differences in immunogenicity.¹²

Pharmacovigilance and Postmarket Surveillance

Postmarketing surveillance is critical in detecting rare adverse events (AEs) or spikes in immunogenicity for both biosimilars and reference-biologics.¹³ Postapproval safety monitoring employs 2 detection systems: spontaneous reporting systems (SRSs) and active surveillance (AS) systems. SRSs are passive methods of reporting, as they rely on voluntary reports from HCPs, pharmacists, and patients.¹³ SRSs are potentially useful for biosimilars as these products are sensitive to variables associated with manufacturing processes and can detect emergent safety issues related to changes in product quality throughout the product lifecycle. SRSs are limited by the inability to accurately quantify the incidence of risks for a product as the total number of treated patients is not identified.¹⁴ AS employs a retrospective analysis of medical records, drug/disease registries, and AE monitoring.¹³ AS methods are suited to identifying multiple potential links to safety signals. When complemented with clinical and scientific algorithms, they can be used to prove causality.¹⁵

In the United States, SRSs are managed through the FDA's MedWatch program and reporting can originate from a variety of sources.¹⁶ The FDA Adverse Event Reporting System (FAERS) database identified patients as the reporters of serious AEs in 41% of reports, HCPs in 36% of reports, and pharmacists in 3% of reports.¹⁷ Detection requires identification of the specific product(s) administered to patients and is complicated by products from several manufacturers sharing identical nomenclature and/or coding.¹⁶ Delayed immune reactions, due to formation of antidrug antibodies, further complicate reporting through a significant time lag between administration and appearance of serious AEs, obfuscating the association of a specific product with the AE.¹⁸ The delay in AE may further affect attributing the reaction to a specific product if the patient has been switched between biologics or lots of a biosimilar product.¹⁹ Despite these limitations, SRS AE reports can be a means to early identification of product or batch-specific issues, a critical function in pharmacovigilance of biologics where multiple manufacturers develop products with clinically similar active substances.¹⁶

US Market Impact

The introduction of biosimilars into the US biologics market has the potential to drive cost savings and increase patient access. Although the United States lags Europe in availability of biosimilars, the US

biosimilar market has the potential to be the largest in the world.²⁰ Estimates for US cost savings range from 5-year savings of \$256 million²¹ to \$54 billion between 2017 and 2026.²² Potential for cost savings in the US healthcare system is partly due to market competition generated from biosimilars.²⁰ Although the market holds substantial promise, the expectation for savings from biosimilars to be similar in scale to that gained from generic chemical drugs may be misguided due to several market differences. Biosimilars have higher development costs and manufacturing costs.²³ These costs help to explain why discounts between biosimilars and reference-biologics are typically less than 30% in the European Union compared to 80% or higher for generic chemical drugs.²³

The potential savings being driven by competing products has led to a great interest in developing economic models that can predict the impact of biosimilar use.²⁰ After the adoption of new interventions, budget impact analysis (BIA) became a modeling method commonly used to consider the expected economic changes in a healthcare system.^{24,25} BIAs can be used alone or as a complement to a cost-effectiveness analysis (CEA).²⁵ Many countries incorporate BIA models into formulary listing and reimbursement decision making at national, regional, and local levels.^{20,25} Despite the increasing importance of BIAs in healthcare, they are rarely published, and many have been found to be of poor quality by expert opinion in a systematic review.²⁶ The International Society for Pharmacoeconomics and Outcomes Research (ISPOR) releases guidelines on BIA good practice, improving and evolving models over time.²⁵ Improved analytic models will be necessary for US decision makers and stakeholders to predict the evolving biosimilar market, which is notably more fluid than that of the European Union because of multiple payers, more versatile formulary structure, and many choices in patient health plans.

The European Model

The European Medicines Agency (EMA) established the European regulatory framework for biosimilars in 2005. Somatropin (Omnitrope), a biosimilar recombinant human growth hormone (rhGH), was the first biosimilar approved in the European Union by the EMA in 2006.²⁷ The first in the world, somatropin exemplified the successful establishment of a regulatory pathway for biosimilars. Within this evolving framework, more than 35 biosimilars have been approved by the EMA to date. In the European Union, biosimilars follow a structured, stepwise development process with guidelines developed jointly by the EMA, the Committee for Medicinal Products for Human Use (CHMP), the Biotechnology Working Party, and the Working Party on Similar Biological Medicinal Products.²⁷ Development begins with comprehensive physiochemical analysis of the various levels of molecular structure.²⁸ This is followed by quality assessment of biologic characteristics using *in vivo* and *in vitro* testing. Preclinical and clinical studies are extensive to

the degree of evidence acquired in physiochemical analysis.²⁸ The aim of clinical trials is to address differences in characteristics between biosimilars and reference-biologics, investigating differences in clinical attributes. Postmarket analyses provide sensitive comparative data, becoming an increasingly valuable stage of the developmental process in the European Union.²⁹

There are several key differences between EMA and FDA biosimilar regulatory pathways. The EMA does not have guidelines on assessments for pharmacy-level substitutions, whereas the FDA assesses the interchangeability of biosimilars, regulating pharmacy-level substitutions via state legislatures.²⁷

The European Union has achieved successful adoption of biosimilars into the market, serving as a model for the younger US biosimilar market. Understanding the key drivers of uptake in the European market will be of utmost importance to US regulatory and payer policies. Biosimilar incentive policies, although heterogeneous between individual countries of the European Union, enhance uptake and drive biosimilar market penetration.³⁰ The market for biosimilars is very different from that of generic synthetic drugs, although expectations have been based on experiences of the latter.

There was a poor understanding of biosimilars at the time of their introduction to the EU market. Due to crucial differences in molecular structure (synthesized vs grown) and considerations for batch-to-batch and lot-to-lot variations, immunogenicity, and interchangeability, it became very apparent that biosimilars would require a different clinical and market approach than those for generic chemical drugs. In 2013, the European Commission Project Group on Market Access and Uptake of Biosimilars published a consensus information document³¹ to educate healthcare professionals, patients, and commission organizations about biosimilars.²⁷ These educational documents were disseminated jointly by both reference-biologic manufacturers and biosimilar developers to provide a consensus of unbiased information. Education is crucial for incorporating biosimilars into clinical practice and has been a key factor in regulatory and market evolution. The EMA publishes a European Public Assessment Report (EPAR) for every human or veterinary medicine application, whether granted marketing authorization or not. The EPAR reflects the scientific conclusions of the EMA committee for the assessment, providing evidence for the committee's opinion to approve or deny an application. EPARS do not consist of a single document, instead evolving with time to reflect up-to-date regulatory information. This then delivers a transparent and detailed body of information made publicly available.

To incentivize the incorporation of biosimilars into clinical practice, benefit-sharing models have been used by EU member states. Under such models, savings accrued through the use of biosimilars allows a healthcare system to reinvest those funds in patient care. The exact policies implemented depend on the EU member state, with a wide degree of heterogeneity across the European Union.

Biosimilars are approved by the EMA, receiving market authorization in the European Union; however, availability differs across the separate member states. Funding is necessary to enable patient access to biosimilars due to the relatively high manufacturing and development costs. If a specific biosimilar is available in a given country, however, it is usually due to the decision of the manufacturer and not regulatory or reimbursement bodies. Availability also differs between specific biosimilars. For example, biosimilars of filgrastim that are most commonly funded are, in descending order, Zarzio, Nivestim, Tevagrastim, and Accofil.³² Germany is the only European country to fund and make available all registered biosimilars.³² Pricing of biosimilars is determined by national authorities and in most countries is determined by a combination of mechanisms such as percentage below reference-biologic, free-pricing, market forces, and national tendering.³²

Physician incentives, through pricing and reimbursement, are another key driver of biosimilar uptake in the EU member states. In 2016, France introduced a new measure, rémunération sur objectifs de santé publique (remuneration of public health goals), encouraging physicians to prescribe a minimum of 20% insulin glargine biosimilars.³³ Belgium advocates a union of the pharmaceutical industry, government, and medical sector with the goal of ensuring patient access to use of biosimilars via “Pact of the future” for the patient with the pharmaceutical industry.³² Germany encourages patient access via regionally based quotas for biosimilar prescriptions.³² In Austria and Belgium, there is an incentive for physicians to prescribe biosimilars based on cost-efficiency initiatives.

Although it is difficult to ascertain a quantitative view of the use of biosimilars in the European Union, in general they are accepted and integrated into respective healthcare systems. Funding and various methods to incentivize biosimilar use have been adopted on a national level within the European Union, perhaps indicating growing trust in biosimilars.³⁴

Conclusions

Incorporation of biosimilars into the US healthcare system will require a multifaceted approach targeting provider/patient education, assurance of strict regulatory standards, and financial incentives. Biosimilar development, regulation, and clinical use are very different from those of generic synthetic drugs, perhaps contributing to the hesitancy to accept biosimilars and general unfamiliarity with key concepts. Similar concerns occurred during incorporation of biosimilars in EU healthcare systems.²⁹ Education targeting HCPs regarding variability within biosimilars/biologics, immunogenicity, and interchangeability may aid scientific understanding of the products and instill confidence in regulatory processes. Viewing the successes seen in the European Union, a consensus of information provided jointly by manufacturers of biologics and biosimilars as well as transparency of FDA approval decisions

could prove very impactful in the United States. As the evidence used for FDA approval of biosimilars is of principally analytical rather than of clinical nature, postmarket surveillance will be of mounting importance to facilitating evidence-based decisions of providers.¹² Although there are challenges to the adoption of biosimilars in the United States, there is great promise of market growth and patient access to care through cooperative educational, legal, and economic initiatives. ■

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