Biologics such as monoclonal antibodies are much more complex than small-molecule drugs, which raises challenging questions for the development and regulatory evaluation of follow-on versions of such biopharmaceutical products (also known as biosimilars) and their clinical use once patent protection for the pioneering biologic has expired. With the recent introduction of regulatory pathways for follow-on versions of complex biologics, the role of analytical technologies in comparing biosimilars with the corresponding reference product is attracting substantial interest in establishing the development requirements for biosimilars. Here, we discuss the current state of the art in analytical technologies to assess three characteristics of protein biopharmaceuticals that regulatory authorities have identified as being important in development strategies for biosimilars: post-translational modifications, three-dimensional structures and protein aggregation.


PURPOSE: The regulatory background surrounding biosimilars (biopharmaceuticals that are considered similar in composition to an innovator product, but not necessarily clinically interchangeable); equivalence, interchangeability, and unique considerations associated with biopharmaceuticals; the biopharmaceutical protein production process; scientific facts for use in the policy discussion about biosimilars: the European Union system for biosimilars; and the current status of biosimilars legislation in the United States are described. SUMMARY: An abbreviated regulatory pathway for the approval of biosimilars, and a process for safely demonstrating the therapeutic interchangeability of these proteins, has the potential to provide meaningful cost savings. This economic advantage to patients can translate into important public health benefits. But to date, no formal regulatory process exists in the United States for bringing these drugs to market. In addition, the current tools for fully characterizing biopharmaceuticals are not--in certain cases--well developed, especially for proteins that have complex structures or are heavily glycosylated. In addition, using "similar" but not completely "identical" proteins interchangeably raises concerns about potentiating immunogenicity. The bottom line is that demonstrating therapeutic equivalence and interchangeability for biosimilars is not a straightforward matter--it cannot be based on the same criteria as for conventional small-molecule drugs. The science, while obtainable, is more complex. For example, it is assumed that showing that a biosimilar protein can be safely used interchangeably with an innovator protein would require, at the least, some limited clinical data and interchangeability studies. Notwithstanding the more complex scientific and clinical issues particular to protein products, most believe that a process for enabling the approval of safe and effective biosimilar proteins is not only possible, but an important public health goal. The European Union system for biosimilars may provide a model for anticipating and resolving the scientific and policy issues related to biosimilars in the U.S. However, biosimilars legislation is unlikely to be passed before the 2008 presidential election. CONCLUSION: The legal and regulatory status of biosimilars remains to be resolved in the United States as policymakers address the scientific and policy issues surrounding product manufacturing, patent terms, and clinical use.


PURPOSE: Historical perspective on the use of biotechnology for drug product development, terminology used for biotechnology drug products, potential benefits of biotechnology, applications of biotechnology to drug product development, pharmacy considerations in the use of biopharmaceuticals, and the classification of biotechnology products by the Food and Drug Administration (FDA) are discussed. SUMMARY: Applications of biotechnology to medicine have a long history, and the pace of new applications has accelerated in recent decades. Various terms, including biosimilars, follow-on biologics, and follow-on proteins, have been used to refer to biotechnology products that are highly similar to the reference product, notwithstanding minor differences. New approaches to the production of drug products have been made feasible through biotechnology, facilitating the prevention, cure, and treatment of diseases. Recombinant DNA technology, monoclonal antibodies, and gene therapy are among the applications of biotechnology processes to drug development. Storage, handling, preparation, and administration are among the pharmacy
considerations in the use of biopharmaceuticals. The FDA has not defined or developed a pathway for establishing therapeutic equivalence of biosimilar and innovator products. Payers may attempt to make decisions about therapeutic equivalence in order to reduce costs. CONCLUSION: Considerable confusion surrounds biosimilars. Pharmacists can help resolve the confusion by explaining to lawmakers and health-system decision-makers the terminology and science of biotechnology processes and the implications for use of biotechnology products in the future.


Biosimilars are protein products that are sufficiently similar to a biopharmaceutical already approved by a regulatory agency. Several biotechnology companies and generic drug manufacturers in Asia and Europe are developing biosimilars of tumor necrosis factor inhibitors and rituximab. A biosimilar etanercept is already being marketed in Colombia and China. In the US, several natural source products and recombinant proteins have been approved as generic drugs under Section 505(b)(2) of the Food, Drug, and Cosmetic Act. However, because the complexity of large biopharmaceuticals makes it difficult to demonstrate that a biosimilar is structurally identical to an already approved biopharmaceutical, this Act does not apply to biosimilars of large biopharmaceuticals. Section 7002 of the Patient Protection and Affordable Care Act of 2010, which is referred to as the Biologics Price Competition and Innovation Act of 2009, amends Section 351 of the Public Health Service Act to create an abbreviated pathway that permits a biosimilar to be evaluated by comparing it with only a single reference biological product. This paper reviews the processes for approval of biosimilars in the US and the European Union and highlights recent changes in federal regulations governing the approval of biosimilars in the US.


The development of biologic therapeutics using advanced technology to copy and improve on nature’s design of complex peptides, proteins, and glycoproteins has enabled the treatment of diseases in entirely new ways and brought unique and lifesaving treatments to many people. However, at least in part because of cost pressures, access to these truly amazing products has not been uniformly available; many patients do not qualify for these treatments, or the treatment is postponed until disabilities accumulate. The development of biosimilars -- essentially copies of the original biologic drugs after patent expiration -- allows for wider and, as important, earlier access to these agents because of their lower cost and consequently greater affordability. The development and commercialization of biosimilars can help address unmet medical needs by improving access to well-established therapeutic interventions while improving health-care affordability.


In the European Union (EU), the regulatory policy for biosimilars has enabled different biosimilar products to be marketed through an abridged application, which allows the applicant to submit a reduced dossier. Nevertheless, some manufacturers of biological products that share some characteristics with copies have opted for a full application; therefore, the number and extent of clinical studies required in these cases is increased. Here, we focus on a comparison of recombinant human erythropoietin medicinal products. We analyse and discuss clinical studies submitted to the European Medicines Agency that relate to available biosimilars and biological medicinal products that are authorised with a full dossier. We also discuss the issues of interchangeability and substitution, given that the EU allows each Member State to set their own substitution policies.


Importance of the field: Ever since the formation of the first biotechnology company almost three decades ago, more than 150 biopharmaceutical products have been marketed across the globe. The oldest of these biotechnology-derived products are now at the end of their patent lives, as a result of which, the development of ‘biosimilars’ is increasing. Areas covered in the review: The review highlights aspects in which biosimilars differ from generic drugs. What the reader will gain: The active substance of a biosimilar medicine is similar to the one of the biological reference medicine; however, biosimilars differ from generics
of pharmacological drugs in aspects like size and complexity of the active substance, and the nature of the manufacturing process. The manufacture of a biopharmaceutical product is complex and involves several isolation and purification steps. These procedures are proprietary to the manufacturer of the originator product and hence even minor changes in production can have serious implications in terms of safety and efficacy of the product. Take home message: Biosimilars should not be brought to market using the same procedure applied to generics, and existing and future regulation should prevent inappropriate and automatic substitution of a biosimilar for a reference biopharmaceutical product.

Misra, M. (2012). "Biosimilars: current perspectives and future implications." Indian J Pharmacol 44(1): 12-14. Biosimilars are biological products that are the replicas of their innovator biopharmaceuticals. These are developed after patent expiration of innovator biopharmaceuticals and are submitted for separate marketing approval. In view of the structural and manufacturing complexities of biopharmaceuticals, biosimilars should not be considered as "biological generics". These are rather unique molecules with limited data at time of approval, so there are concerns about the safety and efficacy of biosimilars. This article will address the differences between biosimilars and chemical generics, issues of concern with the use of biosimilars and need of appropriate regulations for their approval.

Stewart, A., et al. (2010). "Addressing the health technology assessment of biosimilar pharmaceuticals." Curr Med Res Opin 26(9): 2119-2126. Abstract The growing number of biosimilars presents challenges to regulatory and health technology assessment (HTA) systems. This paper illustrates these challenges by focusing on biosimilars used in the oncological setting. In particular, discordances between data required by regulatory and HTA authorities potentially deprive patients of effective treatments and hinder optimal resource allocation. Regulatory and HTA authorities need to harmonize requirements to foster the development and widespread use of biosimilars, which potentially release considerable resources. The authors believe that often-inappropriate methodology creates a very real chance that HTA authorities will reject some biosimilars. This would effectively extend patent protection and, in the absence of competitor pressure from biosimilars, result in prices remaining unnecessarily high. The authors propose that HTA organizations should accept pharmacokinetic and pharmacodynamic equivalence between the brand and the biosimilar as a proxy of biological comparability. HTA organizations should then adopt, in the absence of compelling reasons otherwise, cost-minimization analysis (CMA) as the basis of the cost-effectiveness deliberations. In the absence of adequate studies demonstrating equivalent efficacy, a prerequisite of CMA, HTA organizations should require threshold analysis. Once approved, biosimilar manufacturers and regulators should maintain rigorous pharmacovigilance to exclude immunoreactivity or other rare adverse events. Furthermore, cancer centres and trusts should regularly audit and publish the impact of biosimilars on clinical outcomes and resource use. When appropriate, regulatory and HTA authorities should demand revised cost-effectiveness analyses from biosimilar manufacturers. This approach would hone the accuracy of the cost-effectiveness analyses, protect patients and allow health services rapid access to low cost treatments.

Weise, M., et al. (2012). "Biosimilars: what clinicians should know." Blood 120(26): 5111-5117. Biosimilar medicinal products (biosimilars) have become a reality in the European Union and will soon be available in the United States. Despite an established legal pathway for biosimilars in the European Union since 2005 and increasing and detailed regulatory guidance on data requirements for their development and licensing, many clinicians, particularly oncologists, are reluctant to consider biosimilars as a treatment option for their patients. Major concerns voiced about biosimilars relate to their pharmaceutical quality, safety (especially immunogenicity), efficacy (particularly in extrapolated indications), and interchangeability with the originator product. In this article, the members and experts of the Working Party on Similar Biologic Medicinal Products of the European Medicines Agency (EMA) address these issues. A clear understanding of the scientific principles of the biosimilar concept and access to unbiased information on licensed biosimilars are important for physicians to make informed and appropriate treatment choices for their patients. This will become even more important with the advent of biosimilar monoclonal antibodies. The issues also highlight the need for improved communication between physicians, learned societies, and regulators.

PURPOSE: Scientific issues and clinical implications associated with the use of biosimilars (biopharmaceuticals that are similar to an innovator product, notwithstanding minor differences) are illustrated in two examples, botulinum neurotoxins and erythropoietic agents. SUMMARY: Comparison of Botox and Dysport, products that both contain botulinum toxin type A, revealed distinct differences in physicochemical characteristics, approved indications, dosing, and frequency of adverse events. Differentiating between botulinum toxin products on the basis of immunogenicity in the clinical setting would be of value in product selection, and pharmacists could play a valuable role in collecting antigenicity rate data and reporting them to the Food and Drug Administration (FDA) and the manufacturer. Various ethical and practical considerations are associated with the use of erythropoietic agents. The desire to optimize patient care and outcomes must be weighed against the likelihood of obtaining reimbursement for erythropoietic therapy, and reimbursement policies vary from one state to another. Comparing erythropoietic agents requires the use of a consistent and valid definition of treatment response. The definition of response that FDA will accept in the future when evaluating applications for approval of new biosimilar erythropoietic agents and establishing equivalence remains to be determined. CONCLUSION: A variety of scientific and practical clinical issues are associated with the use of biosimilars, including product differences in physicochemical characteristics, reimbursement policies, and the need for valid and clinically relevant criteria for comparing the efficacy and safety of biosimilars and innovator products.


In March 2010, the US passed the healthcare reform bill, including The Biologics Price Competition and Innovation Act of 2009, which established an abbreviated Biologic License Application (aBLA) pathway for the approval of biosimilars. The aBLA pathway may never be used. At the "Business of Biosimilars" meeting in Boston in September, developers of both innovator and generic biologics as well as representatives from the scientific, regulatory, and legal communities noted that, because of unclear requirements for clinical data and the need for public disclosure of proprietary data, manufacturers of generic biologics are unlikely to take advantage of the aBLA process, opting instead for a standard Biologic License Application (BLA). The implications of an unusable biosimilars pathway in the US dampen our already soft outlook for biosimilars. Companies will still develop follow-on biologics, but approved compounds will behave as new branded drugs. Biosimilars in the US are therefore not likely to lead to aggressive pricing, but will more likely mirror current situations where several similar biologics are available. For example, the interferon (IFN) beta-1a products Avonex(R) and Rebif(R), and Betaseron(R) (IFN beta-1b) have all enjoyed >10% price increases for the last several years in spite of their clinical similarities. inThought reiterates its outlook for generic erosion of a typical biologic that projects a loss of revenue of 30% over 5 years compared to the 90% revenue loss for a typical branded small molecule.


Biologics are essential to oncology care. As patents for older biologics begin to expire, the United States is developing an abbreviated regulatory process for the approval of similar biologics (biosimilars), which raises important considerations for the safe and appropriate incorporation of biosimilars into clinical practice for patients with cancer. The potential for biosimilars to reduce the cost of biologics, which are often high-cost components of oncology care, was the impetus behind the Biologics Price Competition and Innovation Act of 2009, a part of the 2010 Affordable Care Act. In March 2011, NCCN assembled a work group consisting of thought leaders from NCCN Member Institutions and other organizations, to provide guidance regarding the challenges health care providers and other key stakeholders face in incorporating biosimilars in health care practice. The work group identified challenges surrounding biosimilars, including health care provider knowledge, substitution practices, pharmacovigilance, naming and product tracking, coverage and reimbursement, use in off-label settings, and data requirements for approval.