Biosimilar/Competitive Biologic FAQs

What is biotechnology and what is its role in biologic medications?

Biotechnology is described as the set of methods and processes that allow the modification of living organisms—or their parts—in order to produce goods or services. Mastery of so-called “recombinant DNA techniques” in the 1970s opened a new phase in “molecular” biotechnology, revolutionizing various fields of knowledge. Recombinant DNA techniques permitted rapid ways to engineer DNA in biological systems to make therapeutic proteins in a laboratory. Biotherapeutic medicines today are mainly produced by such recombinant DNA techniques. This means that living organisms are genetically reprogrammed to produce a protein of interest. For example, for many years, insulin dependent diabetic patients had only insulin extracted from the pancreases of animals. In 1982 came the first human insulin produced by recombinant DNA technology using a culture of E. coli bacteria. This insulin is superior in quality to the animal-derived product and is produced in sufficient quantities to meet demand.

What are biologic medications and how do they differ from chemically synthesized small molecule medicines?

Biologic medications are medicines whose active ingredients are or are derived from proteins (such as growth hormone, insulin, antibodies) and other substances, and are produced by living organisms (such as cells, yeast and bacteria). They are larger and more complex than chemically-synthesized smaller molecule medicines, and their characteristics and properties are typically dependent on their source living organism and manufacturing process. This complexity makes the full characterization of biotherapeutic medicines particularly difficult. Chemically-synthesized small molecule medicines are instead medicines produced through a step-by-step chemical synthesis process. They are derived from
structurally simple chemical compounds with smaller molecular weight compared to biological medications.

**How are biologic medications manufactured?**
Biologic medications are made using living systems, usually by reproducing a protein in a living cell (such as bacterial or mammalian cells). The characteristics of a biologic medicine are strongly dependent on the conditions of the manufacturing process, and it is often said that “the process is the product.” In fact, even small changes in the manufacturing can alter the final product—therefore the production process of a biological medication requires well designed, robust, reliable and well controlled processes. Good manufacturing practices, validation and defined specifications are of pivotal importance to ensure the safety and efficacy of these products over time: biologic medications undergo approximately 250 in-process tests throughout the manufacturing process. It is in fact the manufacturing process itself that imprints unique characteristics into these products.

**How do biologic medications actually work?**
Biologic medications are large molecules often designed to disrupt, trigger or replace complex protein-protein or cell-cell interactions in a patient’s body. For example in the case of diabetes, human insulin produced by recombinant DNA technology—the world’s first biotechnologically manufactured medicine—acts to replace the missing protein in the patient. Biologic medications are thus developed based on a deep understanding of disease biology in the human body, and are targeted to the specific cause or debilitating symptoms of a disease. Chemically-synthesized small molecule medicines, in contrast, are generally less targeted and address less complex mechanisms of action.

**How are the quality, safety and efficacy of biologic medications evaluated?**
Demonstrating, evaluating and monitoring the quality, safety and efficacy of all medicines is important throughout their life cycle. Health regulatory authorities have requirements in place for evaluating such elements, both pre- and post-approval. Companies too have standard operating procedures and good manufacturing practices in place to ensure that only quality, safe and effective medicines are used in the marketplace. With regard to biologic medicines, more sophisticated tools and techniques—that go beyond those applied for small molecule medicines—are necessary to demonstrate quality, safety and effectiveness in the pre-approval phase. This is due to the complexity of such medicines, to the processes necessary to produce them and to their potential to cause unwanted immune reactions. Because of the limited number of patients involved in the clinical trial phase, post-marketing surveillance (as part of a pharmacovigilance) is also a fundamental tool to allow health authorities to continue to assess benefit/risk throughout the life-cycle of a medicine, and potentially detect rare and serious adverse events that were not identified before marketing authorization. Pharmacovigilance can detect new safety signals related to product quality and/or changes in use and prescription patterns. The World Health Organization (WHO) describes a national pharmacovigilance system “as an obligatory investment in the future public health of the territory.” Maintaining a robust pharmacovigilance system relies on consistent and accurate acquisition, integration and analysis of adverse event data. Without such a strong foundation, important safety signals can get hidden, confounded or diluted. While this need for a strong foundation is common to all medicines, it is especially important for biologic medications.

**What are biosimilar medications?**
Biosimilarity means “highly similar” to the referenced innovator product notwithstanding minor differences in clinically inactive components; and where there are no clinically meaningful differences between the biological product and the referenced product in terms of safety, purity and potency.
Biosimilars are “similar” but not identical versions of their innovative biological medicine of reference whose patents have expired. Whereas producing generic versions of off-patent chemically-synthesized medicines is relatively easy—it involves copying a stable chemically-synthesized molecule with a single identifiable structure. Producing a biosimilar is far more complicated due to the complex molecular structure and the unique manufacturing process required for biologic medications. Unlike chemically-synthesized medicines, it is impossible for biosimilars to be exact copies of the reference innovator. Similar biologic medications are also sometimes called:
- similar biotherapeutic products
- follow-on biologics
- follow-on protein products, or
- subsequent entry biologics

**How does the Patient Protection and Affordable Care Act address biosimilars?**

As part of its sweeping overhaul of the American health-care system, the Patient Protection and Affordable Care Act (ACA) granted the FDA the authority to create a regulatory scheme intended to foster the development of generic biologics. The Biologics Price Competition and Innovation Act (BPCI Act), a subtitle of ACA, enables the FDA to approve the registration of biosimilar products that are similar to, and in some cases interchangeable with, products already approved for sale. In essence, the BPCI Act aims to serve a purpose similar to the Hatch-Waxman Act, which provides an abbreviated pathway to approval for generic small-molecule pharmaceuticals, and is the foundation of the generic drug industry. However, the complexity of biologics, and differences between the statutory schemes, present regulatory challenges.

**What is the regulatory pathway for biosimilars?**

Science-based regulatory standards for medications are essential to ensure patient safety. Because of this—and given the complex nature of biologic medications—biosimilars require distinct regulatory standards from those applied to generic medicines. These standards require thorough analytical characterization and quality studies, as well as targeted pre-clinical and clinical development programs, to show high similarity to the reference innovative biologic medication in terms of safety, purity and potency. A scientifically rigorous regulatory approval pathway for biosimilar products should ensure that there are no clinically meaningful differences between a biosimilar and its reference product in terms of safety, purity and potency. Thus, the biosimilar product would be expected to produce comparable clinical results as the reference product. A legislative pathway for biosimilars already exists in the European Union, however the biosimilar pathway in the U.S. is still being defined. The Biologics Price Competition and Innovation Act (BPCI Act) was signed into law March 30, 2010. The BPCI Act amended the Public Health Services Act (BLA approval pathway). The BPCI Act establishes an abbreviated approval pathway for a 351(k) applicant to demonstrate their drug’s Biosimilarity to and/or Interchangeability with an FDA approved innovator’s reference biologic medication. The BPCI Act encourages competition leading to increased access to biological products for patients. In addition to the innovator biologic, the potential will exist for three distinct competing biologic products to come to the U.S. market:

1. Non-innovator biologic (i.e., BLA approved)
2. Interchangeable Biosimilar
3. Biosimilar

Biosimilar products are available in other highly regulated markets, like the European Union, Canada, Australia and Japan. In 2005, the European Medicines Agency (EMA) implemented the first regulatory framework exclusively for the authorization of biosimilars in the European Union. Furthermore, in 2009
the World Health Organization (WHO) developed guidelines to serve as a blueprint for countries in the development and evaluation of biosimilars.

**What does it mean for a biological product to be “interchangeable”?**
An “interchangeable” biological product is biosimilar to the reference product and can be expected to produce the same clinical result as the reference product in any given patient. In addition, for a biological product that is administered more than once to an individual (as many biological products are), the risk in terms of safety or diminished efficacy of alternating or switching between use of the biological product and the reference product is not greater than the risk of using the reference product without such alternation or switch. FDA guidance on the requirements to obtain the interchangeability designation is needed for full realization of the benefits of biosimilars.

**What are some of the key scientific considerations related to biosimilar product development expressed in the FDA draft guidance documents?**
Key scientific considerations expressed in these draft guidance documents include the following approaches:

- The FDA intends to use a risk-based **totality-of-the-evidence** approach to evaluate all available data and information submitted in support of a determination of biosimilarity of the proposed product. The type and amount of analyses and testing that will be sufficient to demonstrate biosimilarity will be determined on a product-specific basis.
- The FDA recommends sponsors use a stepwise approach in developing evidence to support a demonstration of biosimilarity, ensuring that development at each step evaluates the extent to which there is residual uncertainty regarding a demonstration of biosimilarity between the proposed and reference product, and identify next steps to address that uncertainty.
- Advances in analytical sciences and manufacturing technology, including integration of Quality by Design approaches, may facilitate a “fingerprint”-like analysis of therapeutic protein products, and thus may provide appropriate bases for a more selective and targeted approach to subsequent animal and/or clinical studies for the demonstration of biosimilarity.
- The FDA will best be able to provide meaningful input on the extent and scope of animal and clinical studies needed for a biosimilar development program once the FDA has considered the comparative data from structural and functional analyses.

**Could a biosimilar product be compared to non-U.S.-licensed product data?**
All analytical studies, and at least one pharmacokinetics and pharmacodynamics study, must compare the biosimilar product with a U.S.-licensed reference product. However, in order to increase efforts of globalization of the biopharmaceutical industry, the FDA will allow applicants to use a non-U.S.-licensed reference product in certain additional studies, like animal and perhaps phase III clinical data, if the applicant can establish “an acceptable bridge to the U.S.-licensed reference product.” This bridging likely would require a three-way comparison between the biosimilar and both the U.S- and non-U.S-licensed products.

**What are the allowable differences between a biosimilar and a reference product?**
The FDA addresses ways in which biosimilars may differ from reference products. Clinically inactive components may differ, so long as the applicant can demonstrate that there are “no clinically meaningful differences between the biological product and the reference product in terms of safety, purity and potency.” Proposed biosimilars also may have some differences in the design of the “delivery device or container closure system,” provided that the product is otherwise biosimilar, there is no clinically meaningful difference between the products and the applicant can demonstrate adequate
performance data. Biosimilar manufacturers may obtain licensure for fewer than all routes of administration, delivery devices or conditions of use for which a reference product may be licensed. These points are presented with little elaboration, so it is expected that manufacturers will engage in discussions with the FDA in such circumstances.

**Will the competitive biologic/biosimilar show clinically meaningful differences since it is a different product than the innovator branded product?**
Because no two living cells are identical, no two biologics manufactured have identical materials or proceed in the same way. It important to note that while the complexity argument associated with biosimilars is often utilized by branded manufacturers, biosimilar manufacturers may use the same argument to defend the proliferation of biosimilars since branded companies cannot guarantee 100 percent consistency among different batches of biologics.

**Are there different types of biosimilars?**
There are potentially as many types of biosimilars as there are types of reference biopharmaceuticals. These range from relatively simple proteins like the hormone insulin to highly complex molecules such as monoclonal antibodies (mAbs) and fusion proteins.

**How will the biosimilar products be named?**
Now that the Biologics Price Competition and Innovation (BPCI) Act has provided a regulatory guidance pathway for biosimilars, market participants have turned to issues of marketability. One critical issue is whether biosimilars are entitled to the same nonproprietary name as their reference products. A drug’s name significantly influences the degree to which it is embraced and prescribed by health-care professionals, which in turn affects the drug’s financial viability. If a biosimilar’s name matches its reference product’s name, physicians will likely feel comfortable substituting it, and pharmacy systems are more likely to integrate the biosimilar, a particularly significant issue in the case of non-interchangeable biosimilars. Nevertheless, the BPCI Act does not address this issue and leaves an important element of biosimilars development unresolved.

**What are the exclusivity provisions?**
The period of exclusivity for biologics means that no application for a biosimilar product may be submitted to the FDA until four years after “the date on which the reference product was first licensed.” Approval, and thus marketability, of the follow-on product cannot be effective until 12 years after the date the reference product was first licensed by the FDA.

**What obstacles do biosimilars face?**
Biosimilars have to clear three hurdles:

1. Winning FDA approval, which requires a company sponsoring a biosimilar to do extensive laboratory and clinical testing to ensure that the applicant drug works as well as its reference drug without creating new problems for patients;
2. Growing resistance from biotech firms;
3. Getting doctors, payers (including Medicare and Medicaid), patients and pharmacists* to accept biosimilars as safe and effective substitutes for brand name biopharmaceuticals.

*Pharmacists have huge roles to play in getting biosimilars over the third hurdle.

**Will biosimilars lower health-care costs?**
Yes. However, just how much remains unclear. The 2008 Congressional Budget Office estimated a $25 billion reduction in U.S. expenditures on biologics by 2018.

**Will biosimilars change pharmacy practice?**

No. However, in a letter to the FDA regarding biosimilars, the American Pharmacists Association (AphA), National Association of Chain Drug Stores (NACDS) and the National Community Pharmacists Association (NCPA) outlined several ways pharmacists could ensure patients receive maximum benefits from biosimilars while payers realize significant savings. The practitioner groups focused primarily on the issue of the interchangeability between biosimilars and brand name biologics, providing a gateway for automatic substitution. Just as federal law permits—and some states require—pharmacists to substitute therapeutically equivalent lower-cost generic drugs for brand name products without seeking authorization from prescribers, pharmacists might one day have the authority to automatically dispense biosimilars. APHA, NACDS and NCPA also noted that because patients have more access to pharmacists than to any other health-care providers, pharmacy practitioners would be “on the front lines” of tracking patients’ use of and health outcomes with biosimilars. The associations argue that pharmacists need to be fully involved with the introduction of biosimilars because they will be the health-care providers most directly affected by proper and consistent use of biosimilar product names and the processes and logistics needed to prescribe and dispense biologics.

References for FAQ document on Biosimilars
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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.


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. iThought 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.