

Biosimilars: Policy, clinical, and regulatory considerations

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The legal and regulatory status of biosimilars (biopharmaceuticals that are considered similar in composition to an innovator product, but not necessarily clinically interchangeable) is a health policy issue currently under consideration by the Food and Drug Administration (FDA) and U.S. legislators on Capitol Hill. The establishment of a pathway for enabling the approval of biosimilars through an abbreviated regulatory process, and, in certain cases, for demonstrating their therapeutic equivalence and interchangeability with innovator products (i.e., originator), has the potential to provide meaningful cost savings to healthcare consumers and the government that could translate into public health benefits from improved access.¹ To wit, enabling the approval of follow-on proteins through an abbreviated regulatory process, after the intellectual property on the originator protein has lapsed, could enable price competition between similar products. In addition, the follow-on product could presumably be priced lower than the originator as a consequence of the follow-on product's lower development costs. The ensuing

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.

Index terms: Biologicals; Economics; Equivalency, therapeutic; European Union; Immunogenicity; Regulations; United States

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competition among multiple manufacturers, and additional incentives this will generate for innovators to develop improved versions of existing proteins, could generate still more public health benefits.¹ However, the cost savings probably are not as large as some have estimated. Some current estimates, which envision substantial cost savings, extrapolate from experience with small-molecule generic drugs. This is not an appropriate economic comparison given the scientific and clinical differences between protein and small-molecule drugs. But even smaller cost savings, perhaps on the order of 15–30% off of the cost of an originator protein, could be meaningful. This magnitude of savings mirrors the experience seen in protein drug categories that have benefited from multiple product introductions. As such, it may be a more realistic estimate of the potential savings from biosimilars. This more conservative estimate should not dampen enthusiasm for a thoughtful process for enabling the approval of safe and effective biosimilar proteins. Proponents of the creation of an abbreviated regulatory pathway for FDA approval of biosimilars have every reason to view such a process, and the potential for cost savings, as an important public health goal.

Despite these opportunities, legislation is still needed to create a transparent and predictable pathway for the regulatory approval and marketing of biosimilars. Legislative measures are unlikely to be passed before the 2008 presidential election. This owes to the complexity of the issue as well as continued political debate around key questions among other issues—the appropriate patent terms for innovator products, clinical testing requirements for demonstrating interchangeability, and the regulatory process that should be required before biosimilar products are approved. In particular, there is debate as to whether FDA

should be required to delineate up front, presumably in guidance, the agency's requirements for approval of a particular class of biosimilars before approval of the first product. This guidance development process would presumably be modeled after a similar approach currently used in the European Union. Notwithstanding these ongoing policy discussions, the issue of biosimilars is likely to become a priority after the presidential election and could see quick resolution in the form of new legislation creating an approval pathway.

First and foremost, new legislation must balance the need to protect the public health and to provide innovator manufacturers with incentives for product innovation, against the desire for a risk-based regulatory process that does not impose unnecessarily requirements that add substantially to costs while doing little to promote product safety. Most agree that these competing and sometimes overlapping goals can be resolved in carefully planned legislation that has important implications for access, incentives for innovation, and future research and development efforts.²

Regulatory background

Legislation is required because currently no regulatory pathway exists for the approval of biosimilar proteins through an abbreviated regulatory process. This stands in contrast to the situation surrounding small-molecule drugs, where the Hatch–Waxman Act creates an abbreviated pathway for the approval of generic chemical drugs. Hatch–Waxman represented a compromise between the need to establish a minimum period of exclusivity for brand name innovator products in order to provide appropriate incentives for innovation and the need to eliminate a backlog of applications for generic drugs after expiration of the patents for innovator products. The law requires generic

drug manufacturers to demonstrate bioequivalence to brand name products in healthy subjects, according to well-established FDA regulations and scientific principles, but it allows generic manufacturers to rely on an innovator's clinical efficacy and safety data. The approval process requires that the active ingredients in generic and brand name products are “the same,” but the demonstration of therapeutic equivalence and interchangeability through clinical studies is not required. Under Hatch–Waxman, generic products are approved by an Abbreviated New Drug Application (ANDA) and are automatically deemed to be interchangeable with the innovator product unless the FDA specifically states why the newly approved generic product should not be given an AB rating and thus be deemed to be interchangeable.

But Hatch–Waxman legislation does not apply when it comes to protein drugs. For one thing, the relevance of the Hatch–Waxman Act to biopharmaceuticals is limited because it simply does not take into consideration the issues unique to protein drugs. There were no FDA-approved biotechnology drug products approved at the time the Hatch–Waxman legislation was passed. Moreover, no formal scientific framework for evaluating and approving biosimilars has been established to date. From a policy and legal standpoint, Hatch–Waxman is also simply not germane to the vast majority of protein drugs. The FDA approval process for biopharmaceuticals is governed by two different laws and associated pathways, each with different legal standards for approval. A vast majority of biopharmaceuticals are approved through Public Health Service Act (PHS) section 351 and a biologicals license application, although a few biological products (e.g., insulin, some versions interferon, imiglucerase, human growth hormone) are regulated under the Federal Food, Drug, and Cosmetic

Act (FDCA) as a result of historical precedent.^{3,4} Hatch–Waxman only applies to drugs approved and regulated under the FDCA, which includes all of the small-molecule drugs. Because some protein drugs like insulin and human growth hormone are regulated under the FDCA, a special provision—called Section 505(b)(2)—has enabled FDA to approve follow-on versions of these proteins through an abbreviated regulatory process. Specifically, Section 505(b)(2) of the FDCA allows FDA to approve a follow-on version of an established drug, after patent expiration, on the basis of efficacy and safety findings for the innovator product, although these products are not considered interchangeable or substitutable. However, there is no analogous process under the Public Health Services Act. For that reason, to enable the approval of biosimilars for the vast majority of protein drugs, new legislation would need to be created that would apply a provision, perhaps similar to the 505(b)(2) process, to drugs regulated under the PHS.

Some point to precedents for how this process might work as a matter of science, as well as policy. Omnitrope (somatotropin [rDNA origin]) was approved by FDA through section 505(b)(2) of the FDCA through an expedited process that relied on the finding of efficacy and safety for the innovator product (Genotropin), although the manufacturer of Omnitrope (Sandoz) was required to produce some of its own clinical efficacy and safety data. Nevertheless, Omnitrope is not rated therapeutically equivalent to and therefore is not substitutable for any other FDA-approved human growth hormone product.⁵

While section 505(b)(2) of the FDCA provides some regulatory foundation for how an abbreviated regulatory process for biosimilars could be developed as part of the PHS, the Hatch–Waxman Act (known

more formally as the Drug Price Competition and Patent Term Restoration Act of 1984) provides no such insight. As a matter of science and policy, protein drugs are sufficiently dissimilar from small-molecule drugs and require a fundamentally new approach than the pathway contemplated under Hatch–Waxman. In spite of this, there continue to be comparisons made between the Hatch–Waxman process and the desire for a similar “generic” pathway for protein products.^{1,6} Biosimilars are unique in many respects, but fundamentally, they contain large, complex, or long-chain proteins, and FDA has limited experience using standard laboratory equipment like mass spectrometry for comparing similar biopharmaceutical products produced through different manufacturing processes, and by different sponsors.⁷ For these reasons, and others, the agency has consistently maintained that there are no generic biological products. Even under section 505(b)(2), some formal clinical efficacy and safety studies are typically needed for approval of each product. A new process is needed, one that is uniquely specific to the clinical and scientific attributes of proteins. Such a framework probably will be developed in conjunction with legislation for biosimilars.

Unique considerations around proteins

Biopharmaceuticals present unique clinical and scientific concerns compared with conventional drugs (i.e., small-molecule chemicals) because the active ingredients typically are much larger and more complex. Conventional drugs have fewer molecular ingredients, and most small molecules can be completely characterized on the basis of their chemical structures. By contrast, biotechnology products have many molecular ingredients and often are not fully characterized using evaluative tools alone.⁸

Biologics comprise a wide spectrum of complexity, and so these considerations do not apply equally to all products. Simple and short-chain proteins as well as peptides are relatively easy to compare through laboratory assays, without clinical data. But clinical data may be required for prediction of the therapeutic response to long-chain or heavily glycosylated proteins or those with considerable folding. Along this continuum of complexity of proteins, heavily glycosylated proteins and monoclonal antibodies are among the most difficult products to copy. The need for clinical data to fully characterize the clinical performance of a biosimilar will increase as the complexity of the underlying protein products increases.

Another aspect of a protein drug’s complexity emanates from how it is manufactured. Unlike small-molecule drugs, the manufacturing process for protein drugs is inextricably linked to the characteristics and performance of the resulting medicine. Biopharmaceuticals are manufactured in living systems, with the potential for variability in product composition and structure.² Small differences in starting materials and production processes can affect the final product. Modification of even one small part of a protein can make it ineffective or unsafe. Rare but serious immunologic effects could occur that are not detected in preapproval testing with existing tools (in the absence of clinical data). Indeed, there is precedent for circumstances in which undetected changes in the manufacturing of an established protein had serious clinical consequences. This experience underscores the complexity of the manufacturing process and its correlation to the clinical behavior of the final protein product. For these reasons, evidence of the integrity and consistency of manufacturing processes is among the significant factors FDA considers in evaluating protein products.²

Among the unique safety issues that must be considered, immunogenicity is a major concern with biopharmaceuticals because these products are manufactured in living cells (e.g., hamster, rabbit, or bacterial cells) that are considered foreign by the human body. Administration of biopharmaceuticals bypasses some of the body's natural defenses (e.g., injection directly into a vein traverses the skin) and can therefore result in an immune response and the formation of neutralizing antibodies. The use of scientific tools to evaluate immunogenicity is feasible, but these tools are not available for the full range of biopharmaceuticals. Instead, in many cases, it may be necessary to look at clinical data from switching studies to give assurances against formation of immune reactions. In a switching study, patients are switched between the innovator and the biosimilar protein. Such studies involve the use of assays for detection of neutralizing antibodies and the collection of clinical efficacy and safety data, to make sure subjects had a similar therapeutic outcome to what they would have achieved if they had been continued on just one protein drug and not switched between the innovator and biosimilars product. The data are used to determine whether an immunologic response is generated, whether efficacy and safety are affected by the change in products, and if a biosimilar can be given a labeling claim for interchangeable use with the branded comparator product.

Major unresolved issues of policy

In developing biosimilars legislation, the U.S. Congress and FDA will need to address three major issues: (1) product interchangeability, (2) whether there is a need for formal guidance to delineate the regulatory process for each category of protein drugs prior to the approval of the first biosimilars (this is framed as an issue of regulatory transparency

and well as the benefits and rigor of subjecting approval standards to external scrutiny), and (3) data protection (i.e., patent exclusivity).

Decisions about data protection are probably the most contentious of the three issues. Resolution will require a compromise between manufacturers of innovator products, who seek the longest possible patent exclusivity in order to preserve maximum incentives for development and investment, and manufacturers of biosimilars, who seek the shortest possible patent exclusivity in order to enable early competition.

Regarding product interchangeability, therapeutic equivalence and interchangeability for biosimilars cannot be based on the same criteria used for conventional small-molecule chemicals. According to FDA, different large protein products with a similar molecular composition may behave differently in different individuals, and substitution of one product for another could result in serious health outcomes (e.g., a pathologic immune response).⁹ To date, the means by which interchangeability can be established for complex protein products has not been determined by FDA, although it is presumed that FDA would articulate a process in guidance or regulation after the passage of legislation addressing the broader issues.⁹

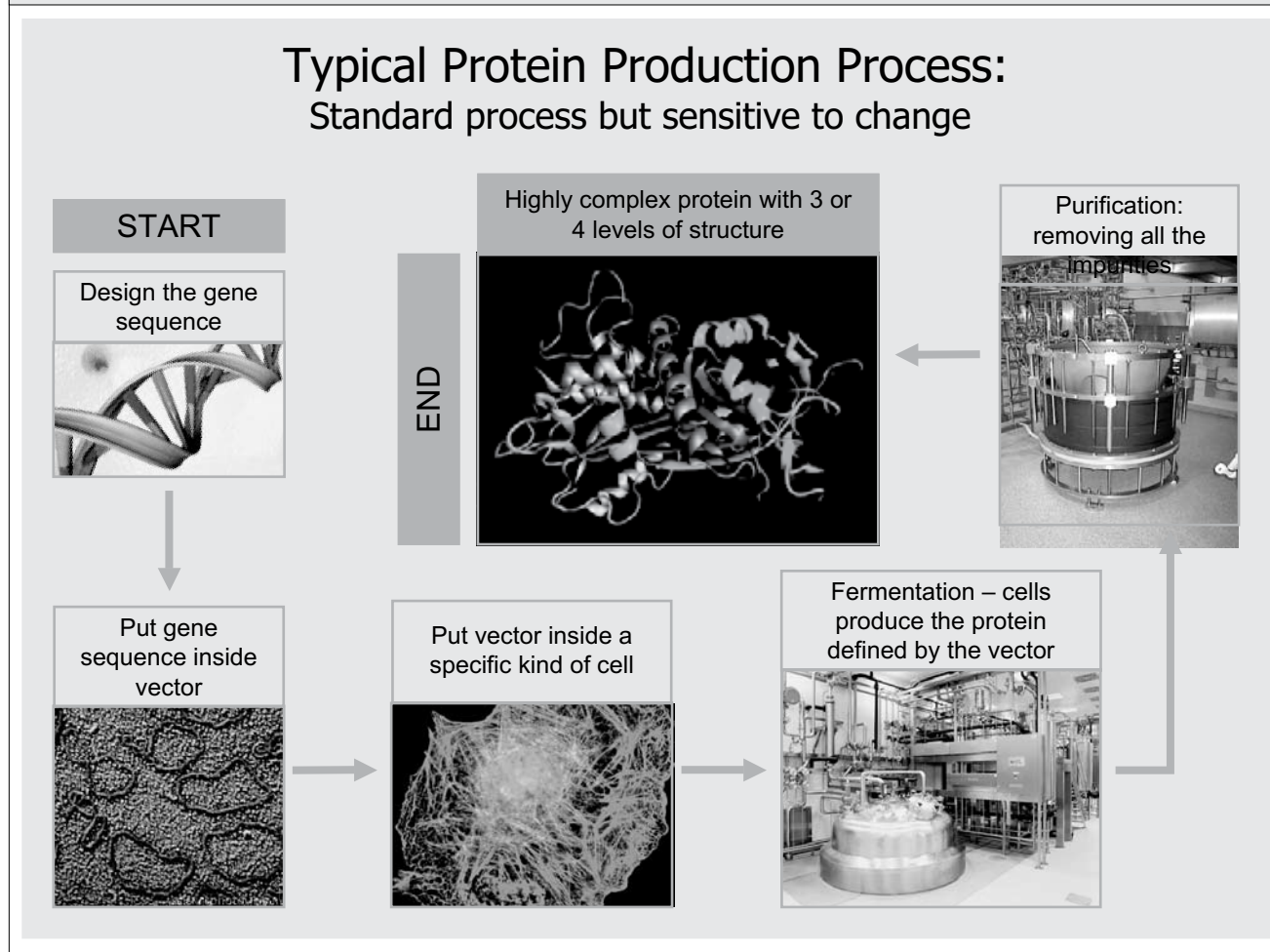
The issue of regulatory transparency deserves greater discussion. Guidance documents will be developed in the future by FDA to address other issues pertaining to not only interchangeability, but also approval standards in specific categories of proteins. The question is whether Congress will direct the agency to develop these guidance documents in advance of biosimilars product approvals, or whether FDA will be given discretion to work internally to design the appropriate regulatory process, and not have to subject these decisions about regulatory architecture to external scrutiny

in each instance. Critics of greater transparency worry that an extensive process of guidance development—similar to the process developed in Europe—would slow the introduction of biosimilar proteins in the U.S. since it could take FDA months to years to develop each guidance document. These arguments have some merit, but may also betray some more complicated motives. For example, it is worth noting that the absence of product-specific guidance will inevitably favor large generic drug manufacturers over smaller rivals, since the large firms are more likely to have the resources and relationships to navigate FDA's regulatory requirements in the absence of specific product guidance that explains the agency's requirements. In this regard, the absence of guidance may serve as a barrier to entry for some low cost producers. To these ends, it should be considered whether excluding a requirement for product-specific guidance is a way for large generic firms that have sophistication in dealing with FDA to freeze out of the process some of their smaller, but perhaps lower-cost competitors.

Special considerations around manufacturing

The typical process used to create protein drugs is standardized, but it is sensitive to change. A gene sequence is designed, and the sequence is inserted into a plasmid or viral vector (Figure 1). The vector is then inserted into a specific type of host cell that produces the protein through a process of fermentation. These host cells are grown in a culture and then transferred to large vessels containing culture medium. Nutrients and oxygen are supplied to keep the host cells alive, and temperature, humidity, and pressure are carefully controlled to produce the desired protein at maximum yield. The protein is separated from the culture medium and cellular proteins, and

Figure 1. Typical protein production process.



impurities are removed during purification, yielding a highly complex protein. This manufacturing process is elaborate and sophisticated, and it is considered intellectual property.⁷ For these reasons, attempts to draft legislation that allows manufacturers of biosimilars to expedite the FDA approval process by engineering around the innovator's manufacturing process have been contentious for manufacturers of innovator products. In addition to the issues of intellectual property, innovator companies argue that the manufacturing process is inextricably linked to the therapeutic qualities of the resulting protein (Table 1).

European Union system as a model

Some believe the European Union system for biosimilars provides a model for anticipating and resolving issues related to biosimilars in the United States. In 1986, the European Union enacted legislation that created a legal basis for approval of "generic" biologicals applications that was similar to the traditional system used in the United States for small-molecule chemical drugs. European authorities realized that the arrangement was inappropriate for biological products. Among other things, there was concern that it provided no assurance that the

active substances were the same in biosimilars and innovators. There was also no assurance that published scientific literature relating to innovator products was relevant to biosimilars. The system was abandoned because of concerns about public safety.

The European Union reworked its system for approval of biosimilars, with basic provisions for governing "similar biological medicinal products (biosimilars)" that went into effect in 2003 and remain in place today.¹² Data protection is provided for 10 to 11 years, and a process for making determinations about interchangeability and supporting clinical data

Table 1.
Scientific Facts for Use in the Political Debate about Biosimilars^{2,7,10,11,a}

Political Statement	Scientific Facts
Biosimilars are identical to the innovator product that they are designed to match.	Biosimilars may be similar to the innovator, but they are not identical. "It is not expected that the quality attributes ... will be identical," per EMEA guidelines.
Innovator product composition varies from one batch or lot to another.	Batch-to-batch variability is a characteristic of all biological products, including innovators and biosimilars. Variability is unique to each product and carefully restricted by FDA. Limits of acceptable variability are defined by clinical experience.
Laboratory data can predict what will happen in the clinical setting, so clinical data are not needed for biosimilars.	Laboratory tests are not sufficiently sensitive to predict clinical response to biosimilar or innovator products. Clinical data are needed to ensure that the efficacy, safety, and immunogenicity are similar (neither worse nor better) for biosimilars and the innovator.
Manufacturing process changes are made frequently for innovator products without supporting clinical studies.	FDA requires clinical data to support certain manufacturing process changes. Significant manufacturing process changes are supported by clinical study data.

^aFDA = Food and Drug Administration; EMEA = European Medicines Agency.

requirements was established. The process is different from that used for the approval of generic small-molecule chemical drugs. The European Union system for approval of biosimilars involves a combination of primary and secondary legislation and requirements for a guidance process. Guidance documents with detailed product-specific requirements must be issued through an open public process, with participation by expert committees, national authorities, the scientific community, and industry. Preclinical and clinical research is required for all biological products in Europe. The European Union system for biosimilar approval devotes special attention to immunogenicity concerns and to post-marketing testing and surveillance for safety

problems. Biosimilars are not considered "generic" equivalents of innovator products—in other words, they are not assumed to be fully interchangeable. To date, two biosimilars (both human growth hormone products) have been approved and one product (interferon alfa) has been rejected in Europe.¹³

The European experience with biosimilars is of great interest to American policymakers because patents for drugs tend to expire earlier in Europe than in the United States. European manufacturers with expertise in biopharmaceuticals already have begun to seek approval for biosimilars, and the collective experience with biosimilar drugs in Europe could provide a basis for understanding their use in the U.S.

What's next

Multiple bills to address a pathway for approval of biosimilars currently are under consideration in the U.S. House of Representatives and the Senate, although none of these legislative measures appear likely to come up for a final vote and passage before the 2008 presidential election. While the need for biosimilars legislation has been largely accepted by members of the Republican and Democratic parties, several sticking points remain to be resolved, including data protection, interchangeability, and clinical research requirements. Some of these unresolved issues turn on matters of science, but it is data protection that remains perhaps the most profound point of policy disagreement. At one point, members of both parties agreed on 12 years of patent exclusivity. However, lobbyists from the generic drug industry balked at that time frame, hoping that a unified Democratic government after 2008 might be able to shorten the duration of patent exclusivity to 10 or 8 years, thus enabling faster entry of biosimilar products after initial approval of the innovator protein.

As for the FDA's handling of biosimilar products, concerns about safety will remain their primary focus. The agency is likely to take a conservative approach and in some cases, ask for a substantial amount of clinical safety and efficacy data before approving biosimilars, especially for the most complex proteins. Policymakers and clinicians in the United States have the advantage of time in deciding how to best address these issues. There are few biopharmaceutical patents set to expire and few biosimilar products for which approval might be sought in the near future. Scientific information for use in guiding decisions about the approval of biosimilars will continue to evolve in the coming years and might help resolve current issues and better inform our decisions.

Conclusion

The complexities of biopharmaceuticals present U.S. policymakers with a challenge in developing legislation to address the legal and regulatory status of biosimilars. Experience in Europe can provide lessons to guide decision-making.

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