

Developing the Nation's Biosimilars Program

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Biotic products developed over the past three decades and approved by the Food and Drug Administration (FDA) now provide important therapeutic options for a variety of serious clinical con-

ditions (see graph). Therapeutic biologics such as genetically engineered recombinant proteins and monoclonal antibodies represent a large portion of newly approved therapies for conditions such as chronic inflammatory diseases and cancer. Biologic enzyme-replacement therapies provide clinical benefits in previously untreatable genetic disorders. Although typically more structurally complex than the small-molecule drugs more prevalent in today's market, biologics vary in complexity from cellular therapies to small, highly purified proteins. Unfortunately, access to such products may be limited, not infrequently because of their cost.

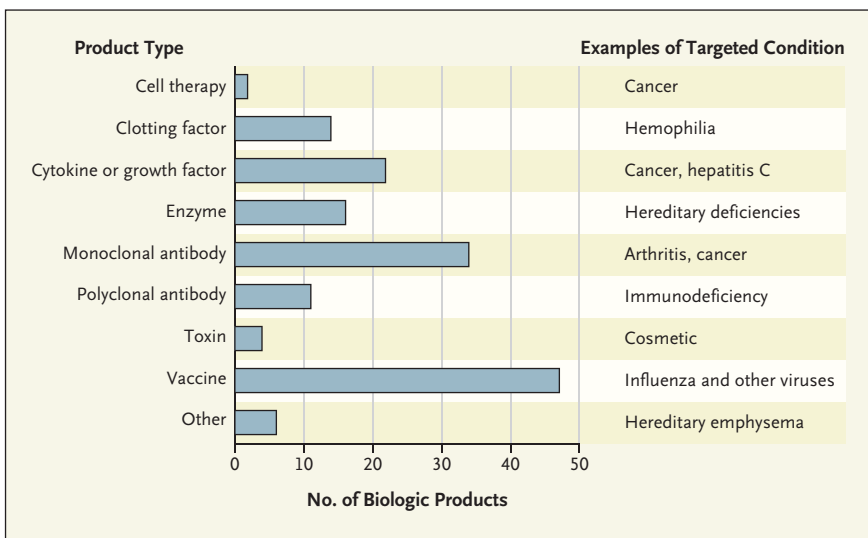
To improve access, Congress

passed the Biologics Price Competition and Innovation (BPCI) Act of 2009, authorizing the FDA to oversee an "abbreviated pathway" for approval of biologics that are "biosimilar" to already-approved products.¹ Utilizing knowledge from the reference products, the abbreviated pathway will eliminate unnecessary (and therefore unethical) testing of biosimilars in animals and humans.

Since 1984, U.S. laws regulating nonbiologic products have allowed an abbreviated approval pathway, permitting the rapid approval of thousands of less expensive generic drugs based on comparisons to reference drugs and dramatically increasing medi-

cines' affordability. In 2009, almost 75% of small-molecule prescriptions dispensed in the United States were for generics, and the approval of a generic drug resulted in average savings of 77% of the product's cost within 1 year. Although cost reductions for biosimilars probably won't be as large, the Federal Trade Commission predicts that their availability will significantly reduce biologics' cost and increase their accessibility.²

Reconciling the science of biosimilar development with the new regulatory framework required by the BPCI Act presents the FDA with numerous challenges. First and foremost, the agency must establish scientific criteria that address the key question: how similar is similar enough when it comes to the substitution of complex biologic drug products in clinical practice? The complex structures of biologic products



Numbers of FDA-Approved Biologic Products of Various Types Available for Treating or Preventing Various Conditions.

The numbers are based on proper names for therapeutics from the Drugs@FDA Web site and the Center for Biologics Evaluation and Research list of biologics (www.fda.gov). The examples of targeted conditions are general, and specific product indications should be based on product labels.

are usually not easily characterized (see diagram). Generally, therapeutic proteins must have a specific set of structural features (e.g., amino acid sequence, glycosylation, protein folding) essential to their intended effect, and slight modifications can affect their performance in humans. In addition, inadvertent chemical modifications can affect their immunogenicity.

Fortunately, progress in the characterization and understanding of biologics now permits demonstration that some products are highly similar to a reference product. Furthermore, the FDA's experience with biologics provides important relevant knowledge. Since the mid-1990s, for example, physicochemical and functional assays have been used to characterize changes in manufacturing processes for some biologics, and then animal or clinical studies are used to resolve any remaining uncertainties about the comparability of the products

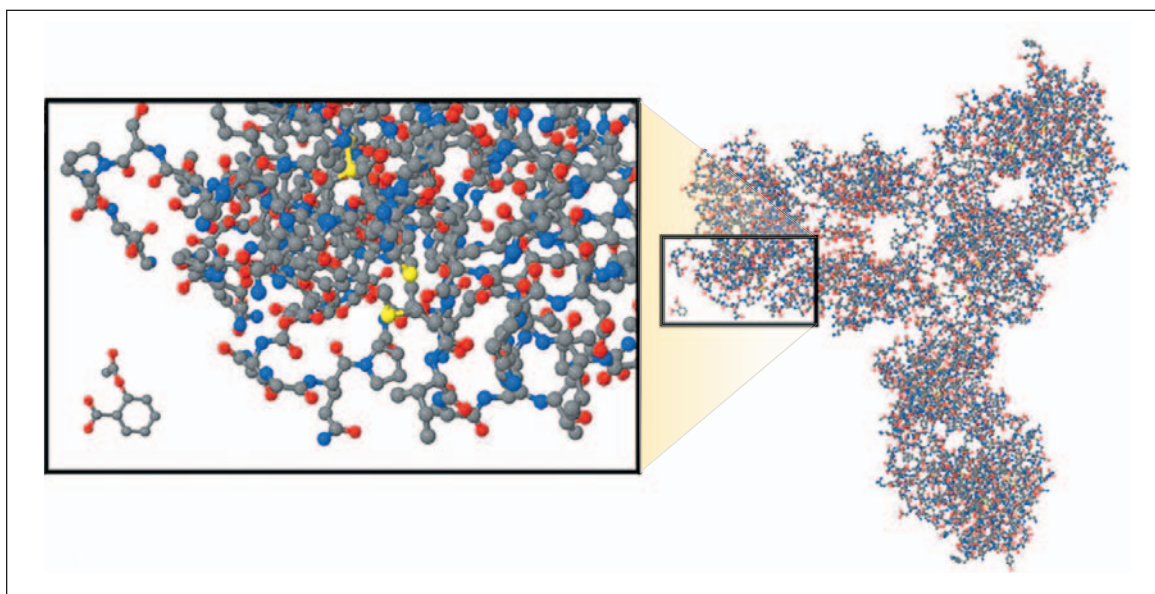
created before and after such changes and to provide sufficient confidence that safety and efficacy are not diminished. The FDA also has extensive experience with abbreviated applications for proteins that are regulated as drugs.³ Moreover, the agency is carefully scrutinizing lessons from the European Medicines Agency (EMA), which published general guidelines on biosimilars in 2005⁴ and approved its first biosimilar in 2006. Initial EMA guidance has suggested product-specific requirements for structural, animal, and clinical studies. Given the complex nature of biologics, it's unlikely that a "one size fits all" systematic assessment of biosimilarity can be developed. Instead, FDA scientists will need to integrate various types of information to provide an overall assessment that a biologic is biosimilar to an approved reference product.

The FDA has traditionally relied on integrating various kinds

of evidence in making regulatory decisions. Such a "totality of the evidence" approach can also be applied to assessing biosimilars, since it seems possible to exceed a current state-of-the-art analytic characterization by evaluating more attributes and combinations of attributes at greater sensitivities with multiple complementary methods. There may be strategies that allow a "fingerprint"-like identification of very similar patterns in two different products. Such strategies were used in supporting the approval of a generic low-molecular-weight heparin product, enoxaparin — which, though it differs from proteins in important ways, is structurally complex. Although additional animal and clinical studies will generally be needed for protein biosimilars for the foreseeable future, the scope and extent of such studies may be reduced further if more extensive fingerprint-like characterization is used.

The totality-of-the-evidence approach faces several challenges. Developers of biosimilars who intend to match reference products more closely will, for example, need to select appropriate source materials and tune their processes carefully. Current approaches to manufacturing process design and improvements in process analytics may be useful.

To help ensure that any additional animal and human testing is appropriately targeted and that biosimilar development plans are optimally streamlined, studies assessing biosimilarity must be carefully tailored to address residual uncertainty. The recent EMA draft guideline on biosimilar monoclonal antibodies⁵ introduces concepts relevant to the design of biosimilarity studies, including the use of populations,



Comparison between a Biologic Monoclonal Antibody and an Aspirin Molecule.

An approximately 800-fold difference in size necessitates magnifying the boxed area to clearly identify the aspirin molecule on the lower left. The antibody structure was taken from the RCSB Protein Data Bank and has the identifier 1HZH.

pharmacodynamic markers, and end points that are sensitive to the potential differences between products. The guideline thus suggests an increasing alignment with the totality-of-the-evidence approach favored by the FDA. This approach, along with the FDA's experience with fingerprint-like characterization of complex products, will be essential in designing a U.S. biosimilars policy that encourages development of biosimilars, emphasizing the use of innovative technologies.

The new pathway will require a new paradigm for sponsor-FDA interactions. To provide the best advice on the scope of any required animal and human studies, the FDA should already have completed an in-depth review of comparative analytic characterization and in vitro data. Although the agency frequently meets with sponsors before they submit investigational new drug applications, a more

extensive product review will be required to determine how much additional data are needed for a biosimilar. The FDA is currently considering how such interactions might be structured and how they will affect the user-fee program that Congress has mandated for biosimilars.

The FDA evaluation of biosimilarity must consider the product's complexity, its formulation, its stability, and the usefulness of biochemical and functional characterizations and incorporate these factors into a risk-based approach. The mechanistic understanding of the clinical effect of a biologic and the level of clinical information available about it will also affect the evaluation of risk, and the manufacturing processes may introduce potential variants or impurities that could affect risk. Evaluating biosimilarity with a risk-based approach is scientifically appropriate and familiar to the FDA, whose decisions are commonly

based on reducing residual uncertainty to an acceptable level in any given clinical setting.

Immunogenicity remains a critical factor when assessing biosimilarity, and the FDA will evaluate immunogenicity in a risk-based manner. For example, aggregation of proteins may be associated with higher risks of immunogenicity, and the risks related to an immune response are greater with products that stimulate immunity to nonredundant self-proteins, such as erythropoietin.

The FDA process for biosimilars must include product-specific safety monitoring. History suggests that pharmaceutical companies will make manufacturing-related changes to biologics periodically throughout their lifecycles, and even small changes could affect safety or efficacy. Tracking adverse events associated with the use of reference and biosimilar products will be difficult if the specific product

or manufacturer cannot be readily identified, and appropriate strategies must be developed to ensure the implementation of robust, modern pharmacovigilance programs for biologics.

Under the BPCI Act, biosimilars will also have the opportunity to meet a higher standard of similarity to a reference product — “interchangeability,” reflecting an FDA assessment that pharmacists can make substitutions between biologics without the prescriber’s intervention. A biologic will be considered interchangeable with a reference product if the developer demonstrates that it can be expected to produce the same clinical result in any given patient and that the risk associated with alternating or switching between the two products is not greater than that

involved in continuing to use the reference product.

The FDA will carefully consider what data will be necessary for this purpose and translate that assessment into effective regulatory standards. The agency will also develop standards to ensure that products not deemed interchangeable are not inadvertently substituted for a reference product without the prescriber’s consent. But even without interchangeability, recognition that two products are biosimilar will give clinicians far more information than the mere knowledge that they were developed for the same indication.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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Redesigning Employee Health Incentives — Lessons from Behavioral Economics

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Buried as Section 2705 of the Patient Protection and Affordable Care Act (ACA) is a provision of potentially momentous importance. Beginning in 2014, employers may use up to 30% of the total amount of employees’ health insurance premiums (50% at the discretion of the secretary of health and human services) to provide outcome-based wellness incentives. Such rewards can “be in the form of a discount or rebate of a premium or contribution, a waiver of all or part of a cost-sharing mechanism (such as deductibles, copayments, or co-

insurance), the absence of a surcharge, or the value of a benefit that would otherwise not be provided under the plan.”

This provision represents an attempt to rein in health care costs, to which health conditions associated with unhealthy behaviors, such as smoking, overeating, and not exercising, are major contributors. Projections that the provision would reduce costs arose, in part, from claims that Safeway Supermarkets had achieved flat health care costs from 2005 to 2009 by tying employees’ health insurance premiums to outcome-

based wellness incentives.¹ It later became clear, however, that Safeway’s program began in 2008 — too late to deserve credit for flat costs starting in 2005.²

Although it may seem obvious that charging higher premiums for smoking (or high body-mass index, cholesterol, or blood pressure) would encourage people to modify their habits to lower their premiums, evidence that differential premiums change health-related behavior is scant. Indeed, we’re unaware of any health insurance data that have convincingly demonstrated such effects.