# Looking at the Recent FDA Biosimilar Guidelines

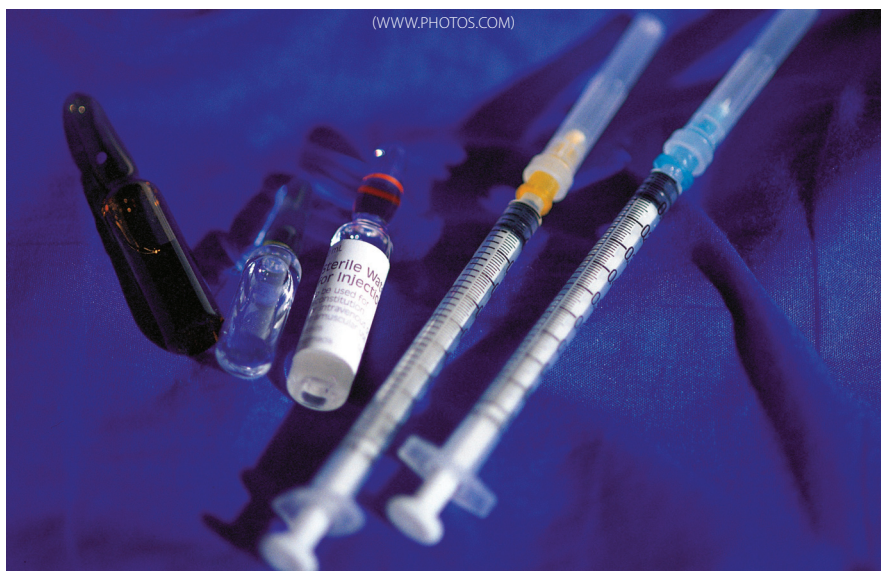
## Immunogenicity Concerns and Extension to Other Classes of Drugs

**by Vera Weinstein**

Small-molecule treatments are invaluable in providing symptomatic benefits for an array of illnesses. However, many serious conditions — ranging from cancer to autoimmune disorders — respond better to more sophisticated complex drugs such as therapeutic biologics and nonbiologic complex drugs (NBCDs). The latter are medicinal, nonbiological products in which the active substance is not a homomolecular structure, but rather consists of a number of different (closely related) structures that cannot be fully characterized. The US Food and Drug Administration (FDA) defines a therapeutic biologic as "a protein derived from living material (such as cells or tissues) used to treat or cure disease" (**1**).

Until recently, pharmaceutical companies in the United States had no procedure to follow when submitting applications for "generic" or follow-on versions of biologic drugs (now called biosimilars). And still, no clear guidelines are available for NBCDs. Despite expiring patents on biologics, this was a complicated issue because even slight changes in protein structure (such as small differences in amino-acid sequence) could cause serious side effects (e.g., immunogenic reactions) in patients.

On 9 February 2012, the FDA released three draft guidelines outlining necessary steps for submitting biosimilar drug applications. The agency's attention to detail came about as a result of past issues seen with complex therapies such as interferons, which produced immunogenicity issues (neutralizing antibodies) in multiple sclerosis (MS) patients (**2**). The guidelines address issues often associated with complex products — such as immunogenicity concerns — by defining specific safety and efficacy testing requirements that will be expected with submissions.


(WWW.PHOTOS.COM)

### Pathway to a Biosimilar Guidance

The FDA began its process of developing regulatory requirements for biosimilars two years ago, when President Barack Obama signed the Patient Protection and Affordable Care Act (PPAC Act) into law on 23 March 2010, amending the Public Health Service Act (PHS Act) .The relevant statutory provisions are also referred to as the Biologics Price Competition and Innovation Act (BPCI Act) of 2009 (**3**). Similar to the Hatch–Waxman Act, which defined an approval pathway for small-molecule generics, the BPCI Act was aimed at a parallel objective for biosimilars.

In one recently released draft guidance, the FDA defines biosimilars or *biosimilarity* as "highly similar to

the reference product, notwithstanding minor differences in clinically inactive components . . . and there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product" (4). The FDA notes the importance of ensuring similarity between a reference product and a biosimilar by taking into account the "structure, function, animal toxicity, and human pharmacokinetics and pharmacodynamics" of the reference product (4). Additionally, "the nature and complexity of the reference product will be considered along with the degree of characterization of the mechanism of action (MOA) of the reference product, the extent to which pharmacokinetic and pharmacodynamic tests predict clinical outcomes, the extent of clinical experience and appropriate endpoints and biomarkers, and the extent of any clinical experience with the proposed product" (4).

Similar criteria are seen in the European Union's regulatory pathway for biosimilars, which was released by the European Medicines Agency (EMA) in 2005. In Europe, companies submitting applications for biosimilars must show that their generic products are closely related to reference medicines and do not have any meaningful differences in quality, safety, or efficacy (5).

Additional guidelines are needed for NBCDs that fall outside the realm of both small molecules and biologics, but the FDA biosimilar guidelines are an important first step in defining regulatory considerations for ensuring affordable patient access to safe and effective therapies.

Because biosimilars are projected to be a multibillion dollar industry, they will have implications for the pharmaceutical industry and patients overall. Integrating affordable biologics into the market will provide more patients with access to life-saving drugs, and companies will be competing to supply them as soon as possible. Additional data may need to be provided with biosimilar applications, depending on the nature of the reference products being reproduced. Such highly complex drugs will require research into the specificities of their make-up — e.g., characterizing method of action (MoA) — and proper testing needed to demonstrate similarity to their reference products.

## Expanding the Guidelines to Other Complex Drugs

Although they are not biological drugs, NBCDs can be just as complicated to characterize as biologics, warranting the need for their own generic guidelines (6). For example, in 1997 the FDA refused to approve generic versions of Premarin tablets (an NBCD used for estrogen replacement) because generic manufacturers could not demonstrate that their products contained the same active ingredient as the reference product. Although sodium estrone sulfate and sodium equilin sulfate were thought to be the only active Premarin ingredients, laboratory and clinical studies suggested that other active ingredients could not be identified. In the FDA statement, Center for Drug Evaluation and Research (CDER) director Janet Woodcock stated, "Based on currently available data, there is at this time no way to assure that synthetic generic forms of Premarin have the same active ingredients as the brand-name drug. This is essential for determining they are equivalent to the brand drug, and is

## Alliance Urges a Cautious Approach for Patient Safety

In response to the US Food and Drug Administration's (FDA) draft guidance on approving biosimilar medicines, the Alliance for Safe Biologic Medicines (ASBM, www.safebiologics.org) submitted comments to the agency in April 2012 outlining recommendations for ensuring that patient safety is at the forefront of the biosimilars pathway. ASBM states that effective implementation must incorporate prudent measures, including

- analytical data and clinical studies to fully characterize biosimilarity and immunogenicity
- traceability measures including unique nonproprietary names for all biologic therapies, transparent product labels, and notification to patients and physicians for clinical assessment and adverse event reporting.

Before designating a biosimilar to be "interchangeable" with its reference product, ASBM says, US regulators must recognize and address that the similarity between reference and biolosimilar products may change over time due to manufacturing or environmental variations.

The organization outlined clear, concrete, and achievable ways to manage risk and thereby prioritize patient safety. Richard Dolinar (ASBM chair) released the following statement as he submitted the coalition's comments to the docket:

"We are pleased with the FDA biosimilar draft guidance, but it leaves a lot of questions unanswered — particularly when it comes to the requirement of clinical studies and pharmacovigilance. There can be no grey area when it comes to patient safety.

"Unwanted immunogenicity is the preeminent safety challenge associated with biological therapeutics and can result in unexpected or sometimes severe adverse effects. The predictive value of animal studies is often insufficient to characterize immunogenicity in humans. Clinical studies, in addition to analytical methods, are necessary to weed out ineffective and unsafe drugs — innovator biologics and biosimilars — before they are ever a risk to patients.

"In the unfortunate situation that problems arise, measures must be in place to accurately and promptly connect a specific patient to a specific product. Our current pharmacovigilance system is not equipped to distinguish a biologic reference product from its biosimilars. Unique nonproprietary names for biosimilar and innovator compounds ensure we will be able to effectively track and trace a product to an adverse event. This must be implemented prior to biosimilar market entry.

The Alliance for Safe Biologic Medicines (ASBM) is an organization composed of diverse healthcare groups and individuals from patients to physicians, innovative medical biotechnology companies, and others working together to ensure that patient safety is at the forefront of biosimilar policy discussions.

also a legal requirement for their approval" (7).

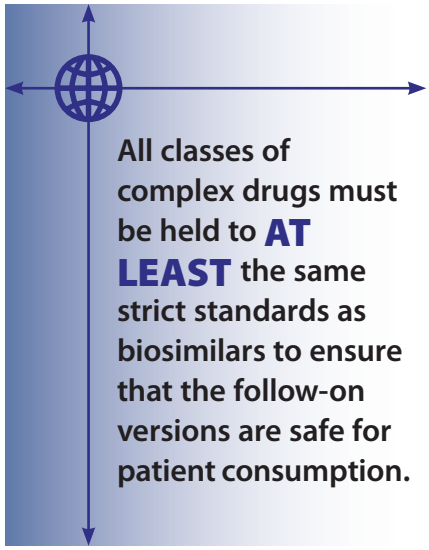
Fortunately, a lot of groundwork for the NBCD guidelines now has been established by the biosimilar pathway — including the need for a stepwise approach to address immunogenicity issues that can arise with these drugs. NBCDs would also need to be evaluated case by case to determine whether clinical trials are necessary if inadvertent chemical and physical changes (such as aggregation) can greatly affect their immunogenicity profile. Already, a generic version of one NBCD has caused immunogenicity effects that were seen only in longer-term clinical trials.

Copaxone injection is an glatiramoid-class NBCD therapy for multiple sclerosis that produces extreme immunogenicity effects when altered. It is a safe and efficacious MS drug produced by Teva Pharmaceuticals as a mixture of polypeptide sequences with immunomodulating activity. Teva pursued development of a follow-on glatiramoid (Protiramer) by introducing slight changes to the Copaxone downstream synthesis procedure. Despite similarity in the basic polypeptide characteristics, and although Teva did not initially detect those in short-term preclinical testing, chronic Protiramer treatment in animal trials over time led to a number of severe side effects: systemic toxicity, extensive fibrosis, organ damage, and eosinophilia. Those results were drastically different from what was seen with the original drug, which has over one million patient years of success (8). No tests exist that can characterize and quantitate the active ingredients of glatiramer (the drug's generic name). Because of that — and Teva's inability to characterize the product's MoA — creating a safe and effective follow-on version could prove to be extremely difficult. A lack of similarity in complex drugs can lead to severe consequences, evident only when tested in long-term nonclinical or adequate clinical trials.

## Safety Cannot Be Compromised

The above examples illustrate significant consequences that minor changes to biologics and NBCDs can cause for patients. In a 2009 article, Eva-Maria Jahn of the University of Duisburg-Essen and Christian Schneider of the Max Planck Institute noted that "as the consequences of such immune reactions to a biotherapeutic drug may lead to potentially serious side effects and/or loss of efficacy, it is essential to adopt an appropriate strategy for the assessment of immunogenicity that involves assay development, and bridging of results to and from clinical development from early on" (9).

Immunogenicity is clearly an important component for consideration, and all complex drug applications should be assessed case by case. All classes of complex drugs must be held to at least the same strict standards as biosimilars to ensure that the follow-on versions are safe for patient consumption. By forming regulatory pathways based on a totality-of-the-evidence approach for highly complex drugs, the FDA and EMA will ensure that patients get access to the best care possible while continuing to ensure that safety remains a top priority.




## References


**1** *Drugs@FDA Glossary of Terms.* US Food and Drug Administration: Rockville, MD, 2 February 2012; www.fda.gov/Drugs/informationondrugs/ucm079436.htm.

**2** *Immunogenicity of Therapeutic Biological Products,* Volume 112. Brown F, Mire-Sluis AR, Eds. S Karger: Basel, Switzerland, April 2003: 3–11.

**3** *Implementation of the Biologics Price Competition and Innovation Act of 2009.* US Food and Drug Administration: Rockville, MD, 10 March 2011; www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/ucm215089.htm.

**4** CDER. *Guidance for Industry: Scientific Considerations for Demonstrating Biosimilarity to a Reference Product.* US Food and Drug Administration: 9 February 2012; www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291128.pdf.

**5** *Guideline on Similar Biological Medicinal Products.* European Medicines Agency: London, UK, 30 October 2005; www.emea.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003517.pdf.

**6** *Immunogenicity of biosimilar Low Molecular Weight Heparins.* Generics and Biosimilars Initiative: Mol, Belgium, 22 April 2011; www.gabionline.net/Biosimilars/Research/Immunogenicity-of-biosimilar-low-molecular-weight-heparins.

**7** CDER. *FDA Statement on Generic Premarin.* US Food and Drug Administration: Rockville, MD, 25 June 2009; www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/PublicHealthAdvisories/ucm169045.htm.

**8** Data on File. Teva Neuroscience, Inc.: Petach Tikva, Israel.

**9** Jahn E, Schneider C. How to Systematically Evaluate Immunogenicity of Therapeutic Proteins: Regulatory Considerations. *New Biotechnol.* 25(5) 2009: 280–286.



***Vera Weinstein,*** *PhD, is director of scientific affairs, CMC Israel, and Europe GBP R&D at Teva Pharmaceuticals, 5 Basel Street, Petach Tikva, 49131 Israel; 972-3-9267267, fax 972-3-9234050; vera.weinstein@teva.co.il.*