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.

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

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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) — and proper testing needed to characterize similarity and immunogenicity” (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 equinol 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
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 Drug@FDA Glossary of Terms. US Food and Drug Administration: Rockville, MD, 2 February 2012; www.fda.gov/Drugs/informationondrugs/ucm079436.htm.


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Safety Cannot Be Compromised
The above examples illustrate significant consequences that minor...