



Biosimilars: new promise for reducing healthcare costs

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INTRODUCTION

After much anticipation, approval of the first U.S. biosimilar medications may be around the corner. Biosimilars hold the promise of reducing healthcare spending by offering lower-cost alternatives to high-priced biologic drugs.

Biosimilars are not generic versions of existing biologics, however. Generic medications contain an active ingredient identical to that in the reference (“brand-name”) product. A biosimilar may contain an active ingredient slightly different from the reference product, as long as the differences are not clinically meaningful.

The Food and Drug Administration (FDA) describes a biosimilar as highly similar to the reference product notwithstanding minor differences in clinically inactive components and for which there are no clinically meaningful differences between the biological product and the reference product in terms of safety, purity and potency of the product.^[1]

LEGISLATION

The Biologics Price Competition and Innovation (BCPI) Act of 2009 addressed the need for an abbreviated approval pathway for biologics^[1]. The previously existing abbreviated new drug application pathway is not suitable for biologics due to their size, complexity, and complicated manufacturing processes.

The BCPI Act requires an applicant to disclose the application and its contents to the sponsor of the reference product within twenty days of filing the application^[2]. This will enable the sponsor of the reference product to immediately begin work on possible patent infringement issues. To avoid this exposure, a company

may decide to forego the biosimilar pathway and instead pursue approval of a copycat biologic via a new biologic license application. This would not result in FDA approval as a biosimilar, but the reduced or delayed risk of lawsuits may be worth it. It would then be up to health care providers and institutions to accept the new biologic on its own merits, without official designation of biosimilarity to an existing biologic.

COMPARABILITY

The idea at the center of a biosimilar application is demonstration of comparability to the reference product^[3]. Manufacturers are well acquainted with this concept from their experience conducting comparability tests following implementation of manufacturing process changes. It is well established that biologics are sensitive to production methods, and that a single product undergoes manufacturing drift as a result of process changes during its lifetime^[4].

The standards to establish biosimilarity will be higher than for comparability following a process change, in part because a manufacturer making a process change has access to valuable proprietary information unavailable to a company developing a biosimilar^[5]. In the European Union (EU), where biosimilars have been on the market for years, several proposed biosimilars were withdrawn after clinical testing failed to demonstrate similar efficacy and safety to the reference product^[6].

FDA GUIDANCE

The FDA has stated that it will use a “totality-of-the-evidence” approach in reviewing biosimilar applications^[1]. The precise requirements will vary from one

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product to another but will include analytical testing, preclinical pharmacokinetic and pharmacodynamic studies, a clinical immunogenicity evaluation, animal studies, and at least one human clinical trial comparing the proposed biosimilar to the reference product. The FDA recommends that applicants follow a stepwise process involving frequent consultation with the FDA. At each step, the applicant should evaluate the data obtained so far and determine what data remains to be collected so that future studies may be tailored appropriately^[3].

Interestingly, clinical studies should be designed to demonstrate neither decreased nor increased activity^[6]. Modern production methods may yield a more potent or effective version of the reference product, sometimes referred to as a “biobetter”, which would not qualify as a biosimilar.

INTERCHANGEABILITY

Beyond the first biosimilars may be interchangeable biosimilars. The concept of interchangeability is analogous to generic substitution for small molecule drugs, such that a pharmacist could substitute an interchangeable biosimilar when filling a prescription for the reference biologic^[3].

As with biosimilarity, identical active ingredients are not required. The exact standards have not yet been determined but the FDA describes interchangeability as a biological product that is administered more than once to an individual, 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^[7].

Companies will likely wait until after the initial biosimilar approval to determine whether or not to pursue interchangeability, rather than apply for both at the same time^[7]. Until then, institutions may authorize the substitution of a non-interchangeable biosimilar for a biologic via therapeutic interchange, as is sometimes utilized for non-equivalent small molecule drugs. The European Medicines Agency does not include recommendations on whether a biosimilar should be used interchangeably with the reference product^[8].

Generic versions of small molecule drugs are sometimes up to 90% less expensive than brand-name products, but the markdown on biosimilars is expected to be about 20–30%^[4]. This lower discount will make it easier for manufacturers of brand-name biologics to compete with biosimilars. However, the overall market for biologic drugs is so large, many billions annually, that the absolute dollar savings may still be substantial.

STATE REGULATIONS

While federal law will identify a drug as an interchangeable biosimilar, state law governs prescription drug substitutions by pharmacists. California senate bill (SB) 598 authorized pharmacists to substitute a biologic with an interchangeable biosimilar, as long as the substitution would not increase the cost to patient^[9].

With a few exceptions, the bill would also have required pharmacists to notify prescribers, or enter into a medical record shared with the prescriber, whether the prescribed biologic or an interchangeable biosimilar was dispensed. Supporters of the bill claim that notification will facilitate tracking of rare adverse reactions and that physicians should know which medication a patient received. Opponents state that the bill creates barriers to biosimilars and that the notification requirement could decrease the number of prescriptions filled with interchangeable biosimilars.

SB-598 was vetoed by Governor Jerry Brown on October 12, 2013. In his communication to the legislature, the governor expressed his support for allowing pharmacists to substitute with interchangeable biosimilars, and that his reasoning for the veto was related to the controversial notification requirement. He concluded that it would be premature to enact legislation requiring physician notification, since the FDA has not yet defined the standards for interchangeability.

EXAMPLE: TBO-FILGRASTIM (GRANIX™)

A newly released product may provide useful experience for the first biosimilars. Tbo-filgrastim is a recombinant granulocyte colony stimulating factor approved to reduce the duration of severe neutropenia in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia^[10].

The manufacturer filed a full biologics license application prior to the establishment of biosimilars via the BCPI Act^[2]. Tbo-filgrastim is not biosimilar to filgrastim (Neupogen™), and published data is not available directly comparing the two products. Filgrastim has several indications for which tbo-filgrastim is not approved: acute myeloid leukemia, bone marrow transplant, mobilization of stem cells for collection, and severe chronic neutropenia^[11]. The EU has seven filgrastim biosimilars, including tbo-filgrastim (Tevagrastim™ in the EU), and all EU products carry multiple indications^[12].

ON THE HORIZON

The first FDA approved biosimilar will probably be a version of filgrastim or erythropoietin, which may be followed by pegfilgrastim, darbepoietin and eventually monoclonal antibodies.^[13] Many unresolved questions remain. Will companies pursue the biosimilar pathway? Or will they prefer to license products via a new biologic application and rely upon providers to utilize them as substitutes for earlier biologics? Transitions of care will be impacted if products are substituted from one care environment to another. How will patients react to biosimilars and how will insurance providers cover biosimilars? The nomenclature has yet to be defined, although it seems likely that the FDA will require a prefix or suffix added to the name of the reference product. Finally, the extent to which biosimilars penetrate the market and the magnitude of healthcare savings remain to be seen.

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