What's New in U.S. Biosimilar-Land?

By Leala Thomas

A lot has been promised with the introduction of biosimilars, but can they really deliver a viable alternative treatment to biologics at a substantial savings? Estimates predict that, in the U.S., healthcare savings could reach between $40 and 250 billion over the next decade just by switching from biologics to biosimilars (Jacoby 2015).

The Importance of Biosimilars

What exactly are biosimilars and why does this class of therapeutics have the potential to take over the biopharmaceutical market? Biosimilars are defined generally as large molecular weight, complex molecules that are produced in living cells through genetic engineering. The U.S. FDA uses the following formal definition: *A biological product that is highly similar to a United States licensed reference biological 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 the safety, purity, and potency of the product*. More simply, it is a biologic that is almost identical to a previously approved biological product, with no clinically meaningful differences in safety or efficacy.

Originator biologics have provided lifesaving treatment for cancer, inflammatory bowel disease, as well as several other diseases. However, the exorbitant cost of a biologic treatment regimen (up to $200,000 per year) is considered cost-prohibitive for many patients and a financial burden on insurance payers. In spite of these exorbitant costs, U.S. sales of biologics account for 50% of global sales value growth and their use continues to increase rapidly.

Progression of Biosimilars

On March 23, 2010, President Barack Obama signed the Biologics Price Competition and Innovation (BPCI) Act of 2009 that granted the U.S. FDA the authority to approve biosimilars and interchangeable biologicals, including recombinant therapeutic protein products, using an abbreviated licensing process. This means that manufacturers are allowed to rely on the FDA's previous determination of the reference biological product's safety, purity, and potency as part of their application file. However, because of the variability in cellular protein expression, each protein produced in batch cell culture will not necessarily be the same. Some microheterogeneity is expected in secondary and tertiary structures of protein molecules produced in these batch cell culture systems, making the end products slightly different (Lemery 2017). To that end, in the last seven years, the FDA has approved only six* biosimilars (Table 1), shattering for the moment the expectation that biosimilars will play an increasingly important role by providing access to innovative therapies and reducing the cost of healthcare in the U.S. (GaBI Online 2017a). This manufacturing challenge, however, does not seem to have deterred the interest of potential participants. Though previously large pharma companies were not interested in producing generics or copies that could dilute their brand reputation and limit their return on investment, they now seem to be getting involved in the biosimilars market, along with small start-ups and biotech firms.

Table 1. The six* biosimilars approved by the U.S. FDA.

Biosimilar	Biosimilar Company	Originator Biologic (Reference Product)	Originator Company
Cyltezo	Boehringer Ingelheim	Humira	AbbVie
Zarxio	Sandoz	Neupogen	Amgen
Erelzi	Sandoz	Enbrel	Amgen
Amjevita	Amgen	Humira	AbbVie
Renflexis	Samsung Bioepis Co.	Remicade	Johnson & Johnson
Inflectra	Pfizer and Celltrion Healthcare	Remicade	Johnson & Johnson

Data sourced from Brennan 2017a, 2017b.
* See Addendum for update.

Why have biosimilars not been more universally accepted by physicians and insurers? Let's take a look at some of the issues.

Outstanding Challenges

A number of significant challenges exist for manufacturers of biosimilars in the U.S. The FDA has not outlined what is required for a biosimilar to demonstrate interchangeability. Current guidance states that an interchangeable product can be expected to produce the same clinical result as the reference product and that there should be no increase in risk or decrease in efficacy (Dalgaard 2013). The benefit to the manufacturer is that the biosimilar could be automatically used as a substitute for the reference product similar to the way generics are substituted for their more expensive brand name counterparts (GaBI Online 2017b). However, to date the FDA has not granted a designation of interchangeability to any of the approved biosimilars.

Another challenge is extrapolating indications. For example, the biologic Remicade is approved in Europe for the following indications: rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, Crohn's disease, psoriasis, and ulcerative colitis. The hope is that any biosimilar to Remicade, once it proves biosimilarity in one indication, would gain approval in all approved indications. According to the FDA, this is potentially possible provided that there is comparability evidence and adequate clinical and scientific justification. Without the ability to extrapolate indications for existing biosimilars, development costs will be higher and the target market will be smaller. Analysts argue, however, that secondary indications typically add only 15–25% to sales revenue, making additional extrapolation testing less advantageous. On the flip side, manufacturers argue that not having all the indications could be perceived as a weakness in the final product.

The need to explain differences between biosimilars and their reference products has also become an issue. Physicians still have a limited understanding of how biosimilars replace an originator biologic. The challenge is to assist them in understanding how biosimilarity works while building confidence that there are no clinically meaningful differences in safety, purity, and potency (Langston 2017). This is the opposite approach from the traditional focus on differentiation from competitors' products.

Using acceptable statistical models for equivalence studies and to tailor phase 3 clinical studies has also been part of ongoing discussions surrounding biosimilars and their development (Welch 2017). If all investigators could agree on the appropriate models with which to evaluate biosimilars, statistical methods could be used to focus clinical trials on any remaining uncertainties surrounding efficacy, reducing the size of large phase 3 trials and ultimately saving time and costs.

What Happens Next?

It seems that the U.S. is still on a learning curve in the development of biosimilars. Regulators want more evidence regarding the quality of biosimilar products and their clinical impact on patients. Which issues will be the most significant? What evidence do regulators want? What new regulations/requirements are on the horizon? At this time, no one seems to know. One thing is certain — biosimilars will remain a therapeutic option and the discussion about their comparability will continue. Investigators hope that in the near future prescribers will develop increasing levels of comfort and experience using these newer therapeutic options in the U.S.

Addendum

Since printing, three more biosimilars have been approved in the U.S., for a total of nine.

Biosimilar	Biosimilar Company	Originator Biologic (Reference Product)	Originator Company
Ixifi	Pfizer	Remicade	Johnson & Johnson
Ogivri	Mylan and Biocon	Herceptin	Genentech
Mvasi	Amgen and Allergan	Avastin	Genentech

Data sourced from Siegel JF and Royzman I (2017). U.S. biosimilar approvals soar in 2017. biologicsblog.com/us-biosimilar-approvals-soar-in-2017, accessed January 29, 2018.

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