Denise Myshko

What's Ahead *for* BIOSIMILARS

Uncertainty lies ahead for the biosimilar market, as manufacturers await FDA guidance.

Biosimilars could represent a multi-billion dollar market in the United States, although some questions remain, including the uptake by physicians and payers, pricing of biosimilars, and how the Food and Drug Administration will review such products.

Alan Sheppard, global head of generics at IMS Health, says many biopharmaceuticals are premium priced and because of this, usage is either restricted by payers or unaffordable for certain patients.

"By making an affordable alternative available, increased usage can result and therapies that were previously restricted could find themselves in a growth environment and achieving a key role in therapeutics," he says

Mr. Sheppard says although development costs of biosimilars are high compared with small-molecule generics — biosimilars cost about $200 million per molecule versus $2 million for small-molecule generics — they are less risky than the development of a new chemical entity.

"Therefore, market conditions are favorable and offer a better return on investment," he says. "This is food for thought for originator biopharmaceutical companies."

Experts say the high costs involved in the development and launch of biosimilars are expected to limit the number of players in the biosimilar market. As a result, erosions in price and volume caused by biosimilars are likely to be lower compared with those created by small-molecule generics.

"The expectation is that there will be fewer biosimilar applicants and so the market will resememble how the generics market looked when there were only one or two generic competitors," says David Fox, partner of the life-science practice at Hogan Lovells. "One would expect that price would hold, perhaps not at pure brand level but it will still hold."

Mr. Sheppard says the main challenge of developing a biosimilar lies in the complexity and cost of development and registration.

"Guidelines for three biosimilar molecules are in place in Europe, and the United States has yet to finalize requirements," he says. "This may result in delays of bioimilars appearing in the United States immediately post patent expiry. There are also other patents related to the biosimilar production process, which could again delay entry."

Mr. Sheppard says one key cost element is the requirement for clinical studies to show comparability with the originator.

"Such studies are lengthy and costly," he says. "This is the main difference between small-molecule generics because bioequivalance is used to show the generic is effectively the same as the originator product. Once approved and similarity is shown, then the biosimilars will have to be promoted to clinicians as they may not be accepted as interchangeable or substitutable with the originator product."

The Biosimilars Law

The Biologics Price Competition act was passed as part of the Patient Protection and Affordable Care Act signed by President Obama in March 2010. The law creates an abbreviated approval pathway for biological products and also extends patent protection for FDA-approved biological medicine for 12 years of exclusivity. The law creates two distinct categories of biosimilar products: products that are "biosimilar" to a reference biological product, and products that are "interchangeable" with the reference product.

Industry experts say interchangeability is something that can evolve over time postapproval as physicians and patients get experience with the product.

The U.S. law allows for an abbreviated clinical development program for biosimilars, but experts stress this will likely be addressed by regulators on a case-by-case basis, depending on the molecule and the case that can be made for similarity.

Experts say regulators will likely look first at how similar the molecule is to the reference product.

"To date, where complex drug substances are regulated as drugs, the FDA has reviewed these products on a case-by-case basis," Mr. Fox says. "But they haven't put it all together into an organized policy statement. A reasonable expectation is that the agency will be appropriately conservative in the beginning of the program to help build confidence in both their ability to analyze biosimilars against the relevant standard and to again ensure confidence in the patient community and provider community."

Thereafter, Mr. Fox says some of the biggest issues the agency will confront are what level of evidence is needed to show that the biosimilar is indeed highly similar to the reference product and what is the right mix of analytical work and clinical work needed.

"Further in the distance is how will the agency assess interchangeability, what types of studies and how large will the studies need to be to resolve whether the product could safely and effectively be substituted," Mr. Fox says. "And there are a range of other downstream issues, including what types of variations on the original biological compound and formulation would be needed for a pioneer product to qualify for a new exclusivity period."

Peyton Howell, president of AmerisourceBergen Consulting Services and senior VP of business development for AmerisourceBergen, says in Europe biosimilar products are priced very close to the innovator biologics similar to branded generics.

"This is an important consideration for manufacturers when evaluating multisource competition because it often means biosimilar companies will have to support the product from a marketing aspect similar to the brand," she says. "Companies can't remove all of the

costs even though the product price will also be lower."

Jeff George, division head at Sandoz, agrees that when it comes to marketing, biosimilars require an approach that is more typically associated with branded pharmaceuticals, such as using a physician field force.

"While price is of course a crucial aspect of our value proposition to our customers, our marketing strategy includes differentiating our biosimilar products by emphasizing their therapeutic quality, delivery mechanism, and patient services," he says. "For example, in the United States, we offer a set of patient services for Omnitrope, our human growth hormone product, that help reduce out-of-pocket costs and make it easier for patients to start on Omnitrope, such as in-home injection training by qualified nurses and a call center. Generally, the appropriate approach for commercial success varies considerably according to product, market, and channel."

Companies Approach Biosimilars

Biopharma companies — including Amgen, Pfizer, Merck — are beginning to consider the biosimilar marketplace. For example, Amgen and Watson Pharmaceuticals announced in December that they will collaborate to develop and commercialize, on a worldwide basis, several oncology antibody biosimilar medicines.

In June 2011, Merck and Hanwha Chemical, a Korean chemical manufacturer, formed an exclusive global agreement to develop and commercialize a biosimilar of Enbrel (etanercept), a drug to treat moderate-to-severe plaque psoriasis, psoriatic arthritis, and moderate-to-severe rheumatoid arthritis.

Pfizer in 2010 entered into a strategic global agreement for the worldwide commercialization with the Indian biotechnology company Biocon for biosimilar versions of insulin and insulin analogue products, for example recombinant human insulin, glargine, aspart, and lispro.

One company that is considered a pioneer in biosimilar development is Sandoz, which has about a 50% share of the biosimilar market in North America, Europe, Japan, and Australia, according to IMS Health. Sandoz markets three biosimilars: human growth hormone Omnitrope, which was approved in Europe and the United States in 2006 and in Japan in 2009; Binocrit, which was introduced in Europe in 2007 to treat anemia; and Zarzio, which was introduced in Europe in 2009 to stimulate production of white blood cells. The company's sales of biosimilar products were up 63% reaching $185 million in 2010.

Company officials say Sandoz's biosimilar products have grown a further 34% through the first nine months of 2011.

"We are fully committed to further extending our lead as the biosimilar market develops and grows," Mr. George says. "We have an outstanding biosimilar pipeline, with eight to 10 molecules at various stages of development and a clear focus on monoclonal antibodies."

Sandoz is developing a biosimilar of rituximab — Roche's Rituxan/MabThera — one of the top three selling biologics worldwide. The company is conducting a Phase II study in patients with rheumatoid arthritis, which aims to demonstrate bioequivalence to the reference product, and is collecting data on pharmacokinetics and pharmacodynamics as well as efficacy and safety. In October, the company initiated patient recruitment for a complementary Phase III clinical study for rituximab in patients suffering from first-line follicular lymphoma.

"Biosimilars present a great opportunity for companies with strong capabilities and know-how in the development and manufacturing of biologics," Mr. George says. "Sandoz is strongly positioned to seize this opportunity, given our significant biotech capabilities and long experience producing high-quality, differentiated generics. Sandoz has more than three decades of experience creating biologics using recombinant technologies and, as part of Novartis, Sandoz benefits from a wealth of expertise and access to development, manufacturing, and commercial capabilities. Cross-divisional synergies within Novartis in biopharmaceutical development, manufacturing, and commercialization are especially valuable as we look to extend our leadership in biosimilars."

Mr. George points out that biosimilar development at Sandoz is based on a simple precept: in the first stage, a proposed biosimilar must be shown to be "highly similar" (United States) or "comparable" (European Union) at the analytical characterization level. Once this is demonstrated, it should be possible to streamline the second stage of preclinical and study requirements.

"We develop and manufacture all of our biosimilars in-house, as we have strong capabilities across the value chain with fully integrated, dedicated biopharma capabilities," he says. "We also collaborate with our colleagues in Novartis Pharma on certain projects. For example, our Phase III clinical study for rituximab in patients suffering from first-line follicular lymphoma is being conducted in coordination with Novartis Pharma."

Mr. George says it's important to keep in mind that there is a significant learning curve.

"At Sandoz, we began development on Omnitrope (HGH) — which became the first ever biosimilar with more than $100 million in sales this year — in 1996 and on Binocrit (EPO) in 1997," he says. "It's interesting to see the high number of new players looking to enter the biosimliar space with partnerships. I think a lot of these companies may be disappointed when their return on investments turn out lower than they had planned, given that many of them will be getting to market significantly later than the first entrants."

He points out that the biosimilars market is relatively new and there is a high barrier for companies to enter this space.

"Entry requires substantial development costs — typically $75 million to $250 million per product — depending in part on the cost of the reference product for clinical trials, and the payback period for industry could be up to 10 years," Mr. George says. "Additionally, developing and producing biosimilars requires substantial expertise and resources that are much different from those needed for small-molecule generics, as well as from those for developing patent-protected pharmaceuticals," he says. PV

EXPERTS

DAVID FOX. Partner, Life Science Practice, Hogan Lovells, a global legal practice. For more information, visit hoganlovells.com.

JEFF GEORGE. Division Head, Sandoz, the generic pharmaceuticals division of Novartis. For more information, visit sandoz.com.

PEYTON HOWELL. President of AmerisourceBergen Consulting Services and Senior VP of Business Development for AmerisourceBergen, which provides drug distribution and related services designed to reduce costs and improve patient outcomes. For more information, visit amerisourcebergen.com.

ALAN SHEPPARD. Global Head, Generics, IMS Health, a provider of information services for the healthcare industry. For more information, visit imshealth.com.