

WHY THE US BIOSIMILARS MARKET WILL BE SLOW TO TAKE OFF

By Sarwar Islam and Lu Chen

AT FIRST GLANCE, IT appears that the US market for biosimilars is ready for takeoff.¹ In March 2015, the US Food and Drug Administration approved Zarxio from Sandoz, a biosimilar version of Amgen's blockbuster Neupogen. Four additional biosimilar applications have been filed for FDA review. And between 2015 and the end of 2019, 39 biologics with combined US sales of \$41 billion, representing 30 percent of the total market, will lose their marketing exclusivity, opening the door to the launch of biosimilar versions.² Some estimates put the US market for biosimilars between \$8 and \$10 billion by 2020.

We believe that these expectations are overly optimistic. While the US market holds great promise for biosimilars, five challenges will hinder its growth in the near term:

- Regulatory uncertainty persists, with the FDA having yet to clearly establish rules for developing and marketing biosimilars, including rules governing interchangeability.

- Payers and policy makers will be cautious about requiring or encouraging patients to be switched to lower-priced biosimilars.
- Building up physician acceptance of biosimilars will not happen quickly.
- Originators—the companies that have developed and marketed the biologics on which biosimilars are based—will deploy strategies to slow the growth of these products.
- Most of the companies developing biosimilars will need to upgrade their biologics-development and product-launch capabilities in key therapeutic areas, which will take time.

The bottom line: the US biosimilars market may not reach critical mass until the mid-2020s. Companies that are developing products based on biologics whose exclusivity will expire before 2020 must therefore develop a plan that does not rely on significant near-term returns. And for those that

have fallen behind or have yet to begin developing biosimilars, the market's likely slow growth creates an opening for products based on biologics whose exclusivity will not expire until 2020 and beyond.

The US: Late to the Game

It is not an overstatement to say that the success of biosimilars globally will largely depend on the US market, which accounts for about half the world's sales of brand-name biologic products.³

The US market has lagged markets in Europe, where biosimilar products have been available since 2006. But the landscape changed with the passage of the Biologics Price Competition and Innovation Act (BPCIA) in 2009. That law established the basic ground rules for developing biosimilars in the US and tasked the FDA with developing comprehensive regulations to govern the market.

There's little doubt that biosimilars will ultimately gain traction in the US. Multiple companies, both traditional generics players and originators, are developing biosimilar versions of blockbusters whose exclusivity will expire by 2020, including Lantus,

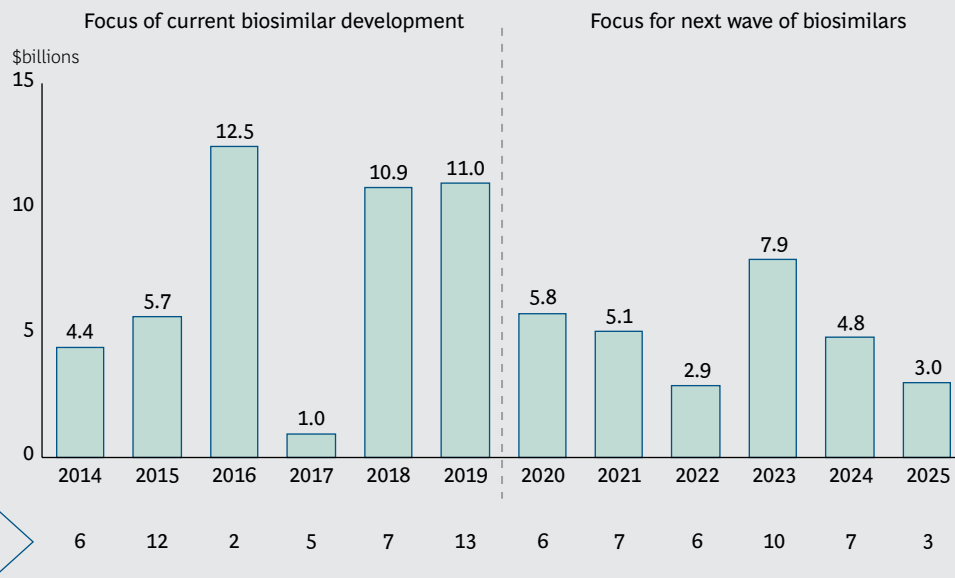
Rituxan, Herceptin, Remicade, Enbrel, Neulasta, Avastin, and Humira.⁴ And a second wave of products losing market exclusivity in 2020 and beyond will create another window of opportunity. (See the exhibit.)

Multiple factors will drive demand for these products. US drug prices are in many cases twice the average in the rest of the world. In addition, biologics are among the most costly drugs on the market. And because many blockbuster biologics treat chronic illnesses such as rheumatoid arthritis and diabetes, their use results in sizable bills to payers and puts a heavy burden on the US health care system. Thus, public and private US payers will ultimately have no choice but to embrace lower-cost biosimilars.

Five Challenges to Growth

So the real question is, How quickly will the market shift toward biosimilars? Consider the generics market for small-molecule drugs. It took about 15 years from the passage of the 1984 Hatch-Waxman Act, which established the generics market, for these products to grab about 50 percent of the market, as measured by volume of prescriptions. And the development of the biosimi-

Numerous Biologics Will Lose Market Exclusivity After 2020



Legend: ■ Cumulative last full year of US sales of biologics facing loss of market exclusivity

Sources: EvaluatePharma; BCG analysis.

lars market outside the US has likewise been slow: the \$2.5 billion in global sales of biosimilars in 2012 accounted for less than 3 percent of the sales of products with expired exclusivity.⁵ In particular, while biosimilars have been on the market in Europe for eight years, uptake in the EU5 (France, Germany, Italy, Spain, and the UK) has been limited, with total estimated sales of around \$500 million and overall penetration rates of 20 to 30 percent (with wide variation across product classes and countries).⁶

Some of the issues that have slowed uptake in Europe—along with some factors that are unique to the US—will have a similar impact on the growth of the US biosimilars market.

Regulatory Uncertainty. The task of establishing a regulatory framework for biosimilars is complicated by the nature of biologic drugs. While the chemical structure of generic small-molecule drugs is identical to that of the original product (the “reference listed drug”), biologics are more complex and are very sensitive to changes in the manufacturing process. As a result, biosimilars are never identical to the original version.

The FDA must develop rules and guidelines for biosimilars that take the differences into account. Moreover, the rules implementing the BPCIA are far from complete, which is creating uncertainty for companies and the possibility of longer-than-expected approval times and higher-than-expected development costs. Issues yet to be resolved include whether companies can sell a biosimilar under the same name as the reference version, and whether biosimilars will require any special packaging to differentiate them from the original.⁷ Sandoz’s Zarxio did receive “indication extrapolation,” meaning that it can be marketed for every indication for which the reference product was approved, without clinical trials being required for each of those uses. But it’s unclear whether all future biosimilars will enjoy the same treatment from the FDA or whether this will be determined on a case-by-case basis, as in Europe.

Perhaps the biggest unknown is how the FDA will make decisions about inter-

changeability. There are two designations under the BPCIA: biosimilar and interchangeable. A biosimilar product is “highly similar” to an existing biologic. For a biosimilar to be deemed interchangeable, the manufacturer must prove that there is no increased risk of side effects or reduced efficacy in patients switched to it from the original version. The advantage of the interchangeable designation is twofold. First, it gives manufacturers one year of market exclusivity for the biosimilar. Second, it increases the odds that payers will institute “mandatory substitution” for the product, allowing pharmacists to substitute it for the reference biologic in states where this practice is permitted.

The requirements for proving interchangeability have not yet been spelled out. But even when the rules are clarified, whether or not to go after the interchangeable designation will present companies with a tough decision. It is likely that the trials required to demonstrate interchangeability will be more complicated and expensive than those involved in demonstrating biosimilarity. More important, if a company’s initial FDA application seeks interchangeability and is rejected, the product’s launch will at a minimum be delayed, in some cases making the product commercially unviable.

Cautious Policy Makers and Payers. The push from policy makers and payers for widespread adoption of biosimilars will be a critical factor in the market’s development. One of the most powerful tools is mandatory substitution, which has led to the widespread use of generic small-molecule drugs in the US and Europe. But we believe that mandatory substitution policies in the US—as in Europe—will not be the norm for biosimilars anytime soon. (See the sidebar, “An Uphill Battle in Europe.”)

In the US, drug substitution is legislated at the state level. While a number of states have passed laws permitting substitution, proposed statutes in other states have failed. But even in those states that allow substitution, the policy is likely to have little impact unless the FDA grants biosimilars interchangeable status. Further compli-

AN UPHILL BATTLE IN EUROPE

Even in the EU, where biosimilars have been on the market for eight years and the pressure from payers to reduce drug costs is far more intense than in the US, mandatory substitution with biosimilars has gained limited traction. Only France and Norway have actively promoted substitution. The law passed in France applies only to patients who are starting a biologic for the first time in a hospital setting—not to those already being

treated with a reference biologic. Meanwhile, the Norwegian government's initial effort to promote the policy was successfully challenged in court by the originator, which argued that the biosimilar was not “generically equivalent” to the reference product. These are all signs that the mandatory substitution policies that have benefited small-molecule generics will be a long time coming in the biosimilars market.

cating matters is the lack of clear guidance and regulations from the FDA governing interchangeability—guidance that might lead to more uniformity in state policies on substitution. Until this materializes, proponents of substitution will have to navigate legislation on a state-by-state basis, which is likely to be a lengthy and arduous process.

Private payers, meanwhile, have yet to assert themselves in policy debates at the federal or state level. But overall we expect them to be cautious when it comes to biosimilars. In particular, they are unlikely to rely simply on an FDA determination that a biosimilar is interchangeable with a reference product. Instead, before they push for the use of such a product, they will likely demand data indicating that its efficacy and safety are equivalent to those of the reference product when used widely in real-world settings.

Among the strongest advocates for biosimilars are large, specialty pharmacy benefits managers (PBMs), which have been very much engaged at both the federal and state levels. However, it remains unclear how PBM revenues and margins will be affected by biosimilars. And if the makers of reference biologics are able to create pricing arrangements that make their products more attractive, that could limit the incentive of PBMs to push for the adoption of biosimilars.

Slow Physician Acceptance. Just as critical as payer support is the degree to which physicians embrace biosimilars. And here we anticipate slow going. Many of the

blockbuster biologics expected to lose market exclusivity by 2020 are treatments for severe diseases such as rheumatoid arthritis and cancer, conditions that physicians will not want to risk treating with less effective drugs.⁸ In general for patients whose diseases are already well controlled with reference biologics, we expect physicians to continue prescribing these treatments. And with mandatory substitution unlikely to become widespread in the near term, physicians will not be compelled to switch these patients to cheaper options.

There are, however, likely to be opportunities among patients who are new to treatment. In particular, some physicians may be open to prescribing biosimilars to patients who would otherwise struggle to afford the copays for higher-priced reference biologics.

However, our conversations with physicians in various disciplines indicate that the adoption rate for biosimilars will differ significantly across specialties. Oncologists, for example, are likely to demand more clinical and real-world data before they are convinced that no differences exist in the efficacy and safety of biosimilars compared with reference drugs. And given the challenge of recruiting patients for oncology clinical trials, even for novel cancer drugs, it will be extremely difficult for the makers of biosimilars to generate the necessary data from randomized trials in the near term. Alternatively, they could wait several years to collect real-world outcomes from places where such biosimilars are marketed. But the end result would likely be the same—a slow adoption rate.

Biosimilars manufacturers also face a critical hurdle in “buy and bill”—the dominant model for biologics purchasing—under which general purchasing organizations negotiate favorable pricing for physicians on products such as oncology treatments; this practice allows physicians to earn a margin based on higher payer reimbursement levels. Companies marketing biosimilars will need to offer similar incentives to physicians, a factor that will further erode biosimilar margins.

Originator Strategies to Slow Market Growth. Biologics originators have been deploying a host of defensive strategies in their fight against biosimilars. One is to get the patent on a biologic drug extended (in one instance, by as many as 15 years); another is to insist that the drug’s manufacturing requirements and clinical data qualify as trade secrets, which—if the FDA agrees—protects any biologic approved before the passage of the BPCIA from competition from biosimilars. Even the launch of the recently approved Zarxio has been delayed in the US by ongoing patent litigation with the originator.

US makers of reference biologics can also use tactics that have been successful in Europe. For example, some originators there have reduced or cut off the supply of their biologics for use in clinical trials by companies developing competing biosimilars. Others have launched trials of a next-generation biologic drug at the same time that the maker of a biosimilar has begun recruiting patients for clinical trials of its product (this can create serious problems in areas such as oncology, where the competition for clinical-trial subjects is already high). Originators have also proactively cut the price of a reference biologic before the launch of a competing biosimilar. And others have launched an improved version of the original biologic ahead of a biosimilar rollout and actively migrated patients to the improved version.

Originators have complemented these defensive tactics with offensive moves. For example, Amgen and Biogen have entered into partnerships with generics and biosimilars companies to develop biosimilars.

Such efforts will give originators greater influence over pricing and the timing of their products’ launch, as well as over the development of the biosimilars market itself.

Manufacturer Skills Gap. To date, makers of biosimilars have had to deal with the development of relatively simple proteins. But even these have thrown up several hurdles, leading to significantly longer timelines and higher costs than were anticipated. The next set of biologics to be tackled are mostly monoclonal antibodies, a far more complex form of protein that will require more sophisticated development capabilities, including the ability to scale up biologics manufacturing, design and recruit patients for complex clinical trials (especially of oncology drugs), and manage the complex regulatory process. Unfortunately, the vast majority of biosimilars players today have either limited or no capabilities in these areas.

Another significant challenge stems from the need to build the right commercial model to bring biosimilars to market—a model that will differ significantly from the approach that has been successful with small-molecule generics, in which the manufacturer contracts with players such as retailers and distributors for a large basket of products. In addition, given the expected lower margins for biosimilars, the commercial model will need to be more lean and more efficient. And it must include elements from the playbook of originator companies, including the ability to build and market brands, generate acceptance in a skeptical physician community, and develop patient and provider support services. Overall, the formidable task of building an entirely new market in the US will require significant commercial prowess and the right balance across marketing, engagement with key opinion leaders, medical education, and sales force. And all this must be done at a cost that matches the economics of the business.

Further, relatively few companies developing biosimilars have experience in therapeutic areas such as oncology and immunology, where the near-term opportunity is

greatest. Building an effective commercial organization in these spaces will require investments and time.

Different Strategies for Different Players

Companies in the biosimilars game must develop strategies that take into account the likelihood that the US market will not experience explosive growth anytime soon. The approach will differ depending on whether the company is a developer of biosimilars competing in the near term, a developer of biosimilars that has fallen behind other players or a manufacturer that has yet to enter the space, or an originator of biologics.

Near-Term Competitors. Players that are developing products based on biologics whose exclusivity will expire before 2020 should focus on three areas over the next five to seven years.

First, they must take steps to carefully manage profitability. A key challenge will be the significant investments required to continue developing biosimilars before the market has reached critical mass. As a result, companies will need to make tricky trade-offs between near-term and long-term profitability.

Consider pricing decisions. It is expected that makers of the first biosimilars marketed in the US will offer discounts of about 20 to 30 percent compared with the reference product. But pricing strategies for individual channels will be complex. Recently issued guidance from the Centers for Medicare and Medicaid Services provides a framework for setting reimbursements for biosimilar products. In order to maximize returns, manufacturers of biosimilars will have to not only strategically set the wholesale acquisition cost but also smartly manage the relative discounts offered in the channels where their products are most likely to be adopted. This will require an in-depth understanding of the economics of each channel, the degree to which biosimilars will be adopted in each one, and the economic impact that buy-and-bill practices have on physician fi-

nances. And all this must be done in a dynamic context in which the manufacturer of the reference drug is likely adjusting discounts to close the price gap with biosimilars and preserve the economics for prescribing physicians.

Second, near-term competitors must take steps to shape the evolving market for biosimilars. This presents a valuable opportunity, but it comes with costs, such as those associated with educating payers, policy makers, and physicians about the benefits of biosimilars. Early entrants will also have to decide whether to advocate for the broad adoption of biosimilars, which will help all future makers of biosimilars, or to push for standards that set a higher bar for approval and adoption, thereby limiting competition with their own products. Depending on which path they choose, manufacturers can explore noncompetitive cross-company partnerships, both industry-wide (through established organizations such as the Generic Pharmaceutical Association) or with a limited group of other early entrants. Similar efforts in the pharmaceutical industry that have focused on improving patient safety and accelerating development could serve as a model.

Finally, companies must sustain the advantage of being early to market and create further barriers to entry for latecomers. This will include building capabilities in scale-up, trial design, pricing, and access. They will also need to create service offerings that strengthen relationships with patients and providers—measures that will be difficult for rivals to copy.

Late Entrants. Companies that have yet to enter the US biosimilars market or that are lagging face real hurdles. But that does not mean latecomers are entirely locked out. Most of the focus to date has been on products whose exclusivity will expire before 2020, but the market is wide open for products that will come after that. Further, there are still opportunities to establish a foothold through acquisitions and partnerships. However, the list of viable targets is short and the price tag on such deals will likely be hefty.

Companies that want to zero in on the potential for biosimilars in 2020 and beyond will have to make several decisions and choices starting now:

- Late entrants must be clear about their ambition. Strategies for building a biosimilars business will vary depending on whether the company wants these products to be a pillar of future growth or an opportunistic add-on.
- They must carefully choose the portfolio of biosimilars that they will pursue. The right mix will depend partly on the company's existing assets and capabilities—and the gaps that it needs to fill—and partly on the level of investments and resources that it can afford to allocate to biosimilars versus other priorities.
- Late entrants need to decide whether they want to build the portfolio and close capability gaps organically—through targeted internal investments—or through strategic partnerships with (or acquisitions of) other players. The answer will depend on the company's starting point and appetite for investments in the near term.
- They must figure out how to create and sustain differentiation in a market that will likely be favorable to early entrants. Potential pathways to differentiation may arise from the ability to speed up development through both innovative clinical-trial design and the leveraging of relationships with key opinion leaders to improve patient recruitment, to rapidly scale up in biologics manufacturing, to exploit existing commercial expertise in specific therapeutic areas, or to create patient or provider services that foster loyalty.

Originators. Originator companies also have some critical choices to make. The most fundamental is whether to lead or slow the development of biosimilars. The first option means accepting biosimilars as a reality and leveraging the company's reputation and capabilities to shape the market—which will put it in a position to

benefit over the long run from the overall expansion of the market for biologics. The second option is to try to limit the biosimilars market. Companies taking this tack will focus on patient safety and the potential unknowns surrounding biosimilars, but they risk criticism for blocking attempts to rein in runaway health care costs.

THERE IS LITTLE doubt that biosimilars will ultimately gain broad acceptance and that the market for biosimilars in the US will be large. What is in doubt is the time it will take for that market to develop. BCG's analysis indicates that there are significant barriers to rapid near-term growth. Both biosimilars developers and biologics innovators must craft strategies that will enable them to thrive in light of that reality.

NOTES

1. A biosimilar is a competing version of an approved biologic product whose safety and effectiveness have been determined by regulators to be similar to those of the original.
2. Based on projected sales in the year prior to the loss of exclusivity. EvaluatePharma, "World Preview 2014, Outlook to 2020," <http://info.evaluategroup.com/ep-wp2014-lp-ep.html>.
3. EvaluatePharma, "World Preview 2014, Outlook to 2020."
4. Ibid.
5. Sarah Rickwood and Stefano Di Biase, "Searching for Terra Firma in the Biosimilars and Non-Original Biologics Market: Insights for the Coming Decade of Change," IMS Health White Paper, 2013, <http://www.imshealth.com/portal/site/imshealth/menuitem.c76283e8bf81e98f53c753c71ad8c22a/?vgnextoid=6e39deacf7832410VgnVCM10000076192ca2RCRD>.
6. A. Sheppard, "Biological/Biotechnological and Biosimilars Market: the Global Outlook with a Special Focus on Europe," 12th EGA International Biosimilar Medicines Conference, April 2014; "Assessing Biosimilar Uptake and Competition in European Markets," IMS Institute Healthcare Informatics, October 2014, <http://www.imshealth.com/vgn-ext-templating/v/index.jsp?vgnextoid=a64de5fda6370410VgnVCM10000076192ca2RCRD&vgnnextfmt=default>.
7. The FDA designated a nonproprietary name for Zarxio when it approved the product but has not yet issued draft guidance on naming.
8. "Biosimilars: A Physician's Perspective," presentation featuring a survey of 376 US physicians, Biosimilars and Follow-On Biologics 2014 Americas conference, 2014.

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