BIOSIMILARS: A GLOBAL PERSPECTIVE OF A NEW MARKET

OPPORTUNITIES, THREATS AND CRITICAL STRATEGIES 2014

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BioWorld Biosimilars: A Global Perspective of a New Market:
Opportunities, Threats and Critical Strategies 2014

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A MARKET IN FORMATION

BIOLOGIC PRICE, LACK OF ACCESS BUILD THE CASE FOR BIOSIMILARS

With their ability to treat many unmet needs, there's no denying the importance of biologics in improving the future of health care across the world. Often viewed as miracle drugs, they offer hope where once there was only despair. They transform patients' lives and provide cures and treatments for diseases that used to be a death sentence or a diagnosis of chronic misery.

All that hope and promise comes at a price – a high price that accounts for much of the revenue biologics produce and that can turn orphan drugs into blockbusters. With some per-patient price tags hitting hundreds of thousands of dollars per year, well above the average cost of small molecule drugs and generics, many biologics are off limits in emerging markets that are facing large, aging populations and an increase in chronic diseases such as diabetes. (See The Daily Cost of Drugs in the U.S., below)

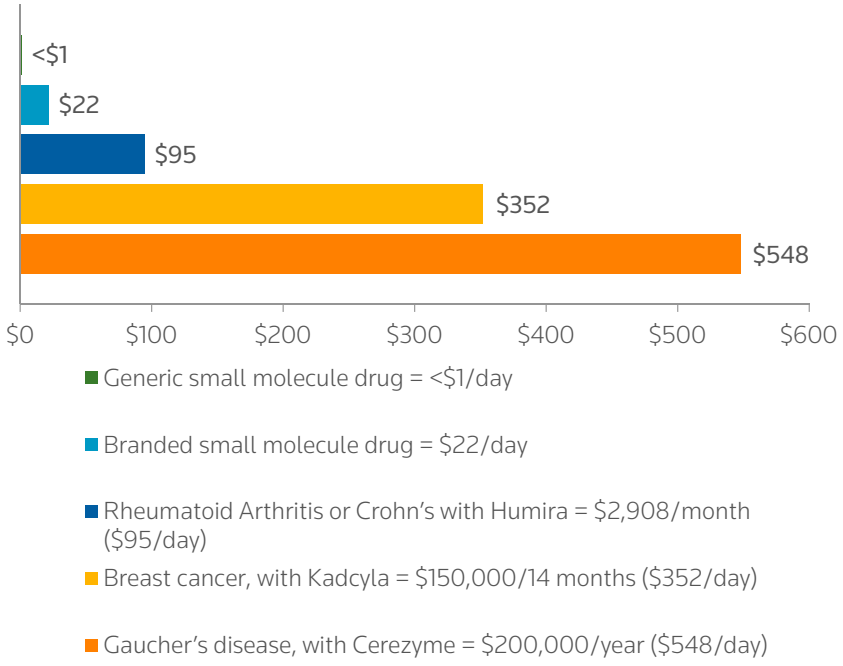
In Peru, for instance, where breast cancer is the leading cause of death for women, the most effective treatments are out of reach for most patients. Genentech Inc.'s Herceptin (trastuzumab) costs about $47,500, nearly eight times Peru's gross national income per capita of $5,880, Public Citizen said.

In China, hemophilia A is a serious health care challenge, given the size of the population. As a result, China accounts for a quarter of the world's hemophiliac A patients who are underserved by existing treatments that are either insufficient or too costly. The two approved recombinant versions available on the market – Kogenate from Bayer Healthcare and Pfizer Inc.'s Xyntha – can cost from nearly $1,000 up to $10,000 per month depending on a patient's bleeding episodes. In more developed markets, Factor VIII is often used as a prophylactic. But due to the price and the patient population, that's not an option in China.

The impact on governments, and the inequities, will mount as more biologics enter the field and existing biologics demand higher prices. Prescription drug sales worldwide are expected to increase 3.8 percent annually between 2012 and 2018, with biologics accounting for a larger portion of those sales. Over the current decade, the global biologics market is expected to grow more than 80 percent – from $138 billion in 2010 to $253 billion by 2020, according to Sandoz International GmbH.

While biologics only make up about a quarter of drug sales, they're more likely to be top sellers. Ten of the world's 25 top-selling drugs in 2012 were biologics. By 2018, four of the top five drugs are expected to be biologics, including Humira (adalimumab, Abbvie Inc.), which is predicted to top the chart at nearly $13 billion in sales due to a 5 percent annual growth rate, according to Evaluatepharma. Of the other potential top sellers, sales of Enbrel (etanercept, Amgen Inc.) will likely remain flat, while sales of Lantus (insulin glargine, Sanofi SA) and Avastin (bevacizumab, Genentech Inc.) are expected to grow 4 percent annually. Broadening the scope to the top 100 drugs, Evaluatepharma predicts 45 will be biologics in 2018, but they'll account for more than half of total sales from that group.

THE DAILY COST OF DRUGS IN THE U.S.



Source: FDA, NHS, Avalere Health, pharmacy pricing

CAUSE FOR ANGST

The numbers are going to get worse for payers as the cost of biologics, both old and new, continues to rise and more biologics come to market. In the U.S. alone, national spending on biologics has increased 15 percent to 20 percent each year and is not expected to slow down any time soon, according to a coalition of 19 institutional investors led by the UAW Retiree Medical Benefits Trust. "These costs could, we believe, impede access for patients and acceptance by providers and insurance companies," the coalition said.

The number of biologics coming to market also is set to climb in the years ahead. While biologics accounted for about a fourth of biopharma sales in 2012, they made up nearly a third of the pipeline. In 2014, 150 biologics were being marketed worldwide and more than 370 were under development. That's good news on the medical front, but it's cause for angst among government and third-party payers already struggling to keep up with the cost of biologics. Some of them are balking at the escalating prices, going so far as to deny or restrict access to specific new therapies.

The UK's National Institute for Health and Clinical Excellence (NICE) refused in August 2014 to approve payment for Roche AG's breakthrough breast cancer drug Kadcyla (trastuzumab emtansine), which at £90,831 (US$152,533) per patient is the most expensive treatment available for breast cancer. While Roche was willing to discount its price, it wouldn't give the 60 percent discount NICE said it would need to recommend Kadcyla, which was developed by Genentech, a Roche subsidiary. NICE based its assessment on interim trial results showing median overall survival was 5.8 months longer in patients treated with Kadcyla than in patients treated with standard-of-care lapatinib and capecitabine. As part of its lifecycle approach to drug development, Roche is positioning Kadcyla as a next-generation biologic for blockbuster breast cancer drug Herceptin (trastuzumab), which is set to lose patent protection in the EU in 2014 and in the U.S. in 2019.

The price of biologics also has affected policy in the U.S. in some instances. The FDA looks the other way when compounding pharmacies market diluted versions of Genentech's Avastin (bevacizumab) for treating age-related macular degeneration (AMD), an off-label use, and Medicare encourages the use of Avastin over Genentech's Lucentis (ranibizumab), which is approved for AMD. When diluted to the concentrations called for in ophthalmic indications, Avastin, at $100 or less per injection, is one-twentieth the price of Lucentis, which sells for about $2,000 per injection.

The price difference between Lucentis and Avastin is serving as a catalyst for some cash-strapped European governments to enact laws that would allow for off-label use even if on-label treatments are available. Italy passed a bill in June 2014, permitting Avastin to be used instead of Lucentis in AMD. A month later, France was following suit, raising fears that the governments were undermining the EU's biologic regulatory standards.

Governments aren't the only ones restricting access to high-priced biologics. In the U.S., third-party payers are kicking some drugs – biologics and small molecules – off their formularies because of the cost. Both CVS Caremark and Express Scripts have become more aggressive about excluding high-priced drugs when there are alternatives – even if the alternatives may not be as convenient for patients.

"Education and understanding are paramount to foster wider use of biosimilar medicines. While they are well understood by EMA regulators, there is significant work ahead of us in improving understanding amongst most other stakeholders."

Joerg Windisch, chairman of the European Biosimilars Group, EGA sector group

PROMISE OF BIOSIMILARS

Rather than forgo the benefits of biologics, governments and payers are counting on biosimilars to revolutionize health care by reducing the cost of important biologics and increasing access to life-saving drugs. For that to happen, the follow-on biologics (FOBs) will have to deliver the power of the reference drugs at a price financially strapped countries can afford and gain the confidence of the marketplace.

Several FOBs are already competing in many parts of the world, but they differ greatly in terms of quality and price, depending on the regulatory scheme under which they were approved. Because the standards vary from country to country, not all FOBs would be considered biosimilars in the regulated markets. As a result, several different terms are being used to describe various FOBs.

Alternatives are biologic copies that haven't demonstrated comparability to a reference product. These are often approved in emerging markets as new drugs or "noninnovators," but they are not considered biosimilars.

Biobetters are biologic copies that are safer, more effective or more convenient than the reference product. In regulated markets, they must be approved as new biologics. However, since they are based on an approved biologic, the risk of failure may be reduced significantly. Another benefit is that they can build on an already established market.

TOP-SELLING BIOLOGICS 2013

DRUG	BIOLOGIC	INNOVATOR	2013 GLOBAL SALES	2014 GLOBAL SALES*	PATENT EXPIRATION
Humira	adalimumab	Abbvie Inc.	$10.7B	$12.3B	EU – 2018 U.S. – 2016
Enbrel	etanercept	Amgen Inc./Pfizer Inc.	$8.4B	$5B	EU – 2015 U.S. – 2029
Rituxan/Mabthera	rituximab	Roche AG/Biogen Idec Inc.	$7.7B	$7.8B	EU – 2013 U.S. – 2018
Lantus	insulin glargine	Sanofi SA	$7.6B	$8.7B	EU – 2015 U.S. – 2015
Avastin	bevacizumab	Genentech Inc.	$7B	$7.2B	EU – 2022 U.S. – 2019
Herceptin	trastuzumab	Genentech Inc.	$6.8B	$6.8B	EU – 2014 U.S. – 2019
Remicade	infliximab	Johnson & Johnson	$6.7B	$9.9B	EU – 2015 U.S. – 2018
Novolog/Novorapid	insulin aspart	Novo Nordisk A/S	$4.7B	$5B	**EU – 2011 U.S. – 2014
Neulasta	pegfilgrastim	Amgen Inc.	$4.4B	$4.5B	EU – 2015 U.S. – 2015
Epogen/Procrit/Eprex	epoetin alfa	Amgen Inc./Janssen Pharmaceutica NV	$3.3B	$3.1B	EU – Off patent U.S. – 2015

* Cortellis forecast
**Novo Nordisk expects other patents will continue to protect Novolog/Novorapid after the drug patents have expired
Sources: Company annual reports, Cortellis Regulatory Intelligence

Biologics are comprised of large (at least 5,000 atoms) molecules that are derived from living cells and manufactured through biological processes. Because of their complexity, the safety and effectiveness of biologics can be significantly impacted by minor differences in the manufacturing processes. Thus, even an innovator product has inherent lot-to-lot variability.

Biosimilars must be "highly similar" to the reference product. While there can be minor differences in clinically inactive components under U.S. law, there can be no "clinically meaningful differences" between the biosimilar and the reference drug in terms of safety, purity and potency. Since a biosimilar relies on prior findings of efficacy and safety for the reference product, it has to demonstrate comparability/similarity to that product in a head-to-head trial in highly regulated markets, where they are approved on a designated abbreviated path. The level of similarity required may differ from country to country. Biosimilars are known as ***biocomparables*** in Mexico, ***regular biologics*** in Brazil and ***subsequent-entry biologics*** in Canada.

Follow-on biologic (FOB) is a broad term used to describe any drug that copies an approved/marketed biologic. Alternatives, biobetters, biosimilars and interchangeable biologics are all FOBs.

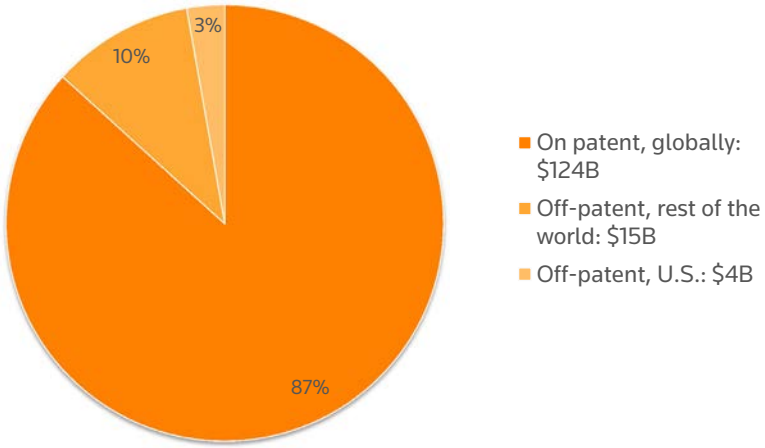
Interchangeable biologics are expected to produce the same clinical results as their reference drug in any given patient. The risk, in terms of safety or diminished efficacy, of switching between an interchangeable and reference biologic must not be greater than from consistent use of the reference product. The FDA anticipates drugmakers would have to demonstrate the sameness of a potential interchangeable through switching trials with the reference drug.

Reference biologics are approved/marketed originator drugs that serve as the model for FOBs. Generally in regulated markets, the reference biologic would be off patent by time an FOB is launched.

Regardless of what they're called, what all FOBs have in common is that they target the top-selling biologics, especially those that have lost patent protection in specific markets. (See Top-selling Biologics 2013)

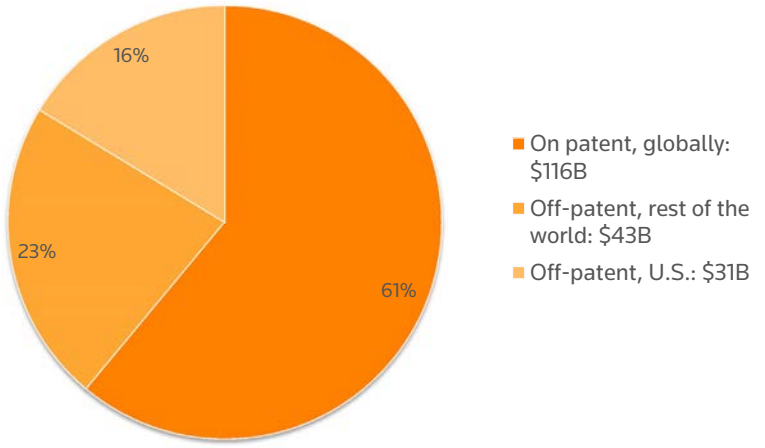
While alternatives may hit emerging markets long before the reference biologic loses patent protection elsewhere, biosimilar launches are expected to come in waves in highly regulated markets like Australia, Canada, the EU, Japan and the U.S., coinciding with patent expirations of the blockbuster biologics. The first wave began cresting in the EU last decade with approvals of filgrastim, somatropin and epoetin biosimilars, all of which fell off patent earlier there

TOTAL GLOBAL BIOLOGIC SALES FOR 2013: $143B



Source: Sandoz International GmbH

PROJECTED TOTAL GLOBAL SALES FOR 2018: $190B



Source: Sandoz International GmbH

than they did in the U.S. Because of the differences in intellectual property (IP) protection and the fact that the U.S. started forming its biosimilar path several years later than the EU, the FDA has yet to approve its first biosimilar.

But the first wave, which includes biosimilars referencing biologics with patent expiries before 2020, is about to hit the U.S. Sandoz filed the first biologic license application (BLA) for a biosimilar with the FDA in July 2014. Its Zarxio BLA references Amgen's Neupogen (filgrastim), which lost U.S. patent protection the previous year. Following Sandoz's filing by a few weeks, Celltrion Inc. submitted a 351(k) BLA with the FDA for Remsima, referencing Janssen Biotech Inc.'s Remicade (infliximab). Celltrion also is challenging Remicade's remaining U.S. patents, which won't expire until 2018. Under the biosimilar user fee agreement, the FDA has 10 months to review a biosimilar BLA before making an approval decision.

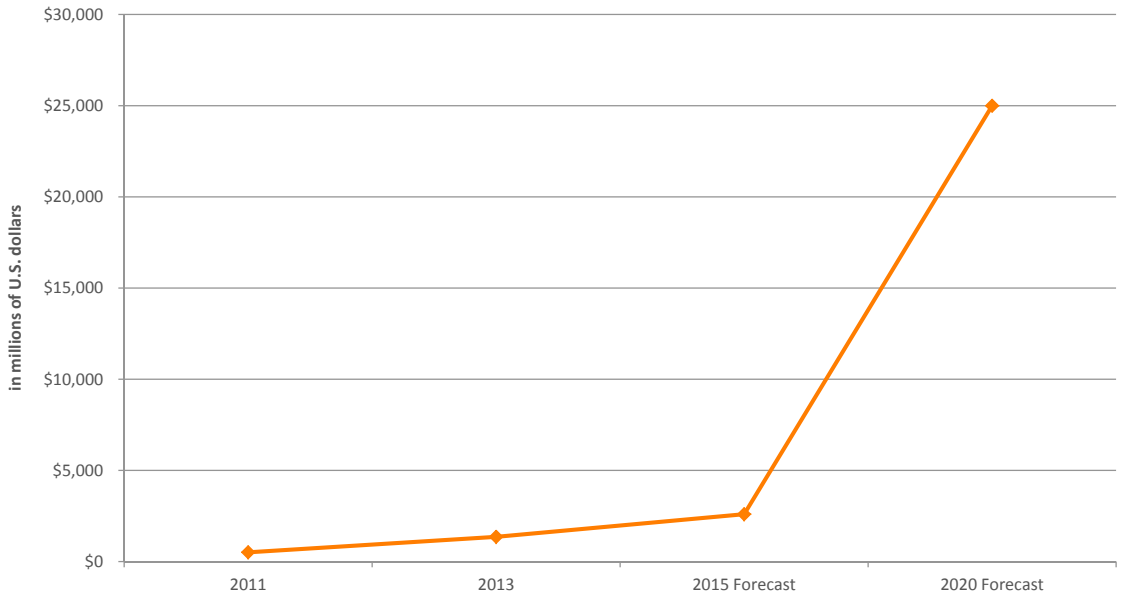
The second wave of biosimilars in regulated markets will be those referencing biologics that lose IP protection in 2020 or beyond. One thing to keep in mind, though, is that some of the FOBS in these waves will not be considered biosimilars in the U.S. (See Waves of Biologic Blockbuster Targets)

Several blockbuster biologics have lost IP protection in the EU and elsewhere. Of the $143 billion in global biologic sales in 2013, $4 billion stemmed from biologics that were off patent in the U.S. and $15 billion from ones that were off patent in the rest of the world, according to Sandoz.

That number will escalate over the next few years. By 2018, $31 billion worth of biologic sales are expected to come from off-patent drugs in the U.S. and $43 billion from off-patent biologics in the rest of the world. And by the end of the decade, Sandoz said, patents will have expired for originator biologics accounting for about $100 billion in global sales. (See Global Biologic Sales)

Although the market for biosimilars is predicted to rise rapidly as patents expire for blockbuster biologics, biosimilar sales are not expected to keep pace with the opportunity, largely due to the complexity of biologics, slow market uptake and regulatory issues. Total global sales of drugs approved as biosimilars in 2011 added up to about $510 million. By 2013, those sales had more than doubled to nearly $1.36 billion. IMS Health expects biosimilar sales to hit $25 billion by 2020, accounting for about a quarter of the $100 billion worth of sales stemming from off-patent biologics by the end of the decade. (See Projected Increase in Biologic Sales, below)

PROJECTED INCREASE IN BIOLOGIC SALES



Source: IMS Health