Threats and Opportunities

The U.S. Biosimilars Market

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Threats and Opportunities

Over the past 20 years, the emergence of biotechnology products has revolutionized the treatment landscape in a number of therapeutic areas. By developing products based on the human body’s own endogenous biological processes, biotech companies have been able to create products with therapeutic potential previously unattainable through traditional small molecule drug development. Now the expiration of the patents protecting these biopharmaceuticals has opened the door to the creation of biosimilars – the biologic equivalent of generic drugs.

Beginning in 2014, the projected sales of biologics going off patent in the U.S. will exceed those of conventional, small molecule drugs. With multiple biosimilar products on the market in the EU and discussion in the halls of Congress over the regulation of biosimilars in the U.S., the biosimilar market is at a critical point in its development. While its potential is huge, a number of critical factors stand to determine, in the near future, just how much of that potential will be realized. As events continue to unfold, both biotech companies and their biosimilar developing rivals need to determine how to best position themselves to respond to the opportunities and threats that these developments portend.

The regulatory, commercial, and technical factors that will shape the future of the U.S. biosimilar market

There are a number of factors that will determine the future of the biosimilars market in the U.S. The first and most significant factor centers around the approval and regulatory framework in which biosimilar developers will need to work. Policies towards automatic substitution, adoption and promotion of biosimilars by third party payers, and the resolution of safety and quality concerns will have an enormous impact on the potential uptake of biosimilars within the U.S. market. Finally, the economic and technical feasibility of continued biosimilar development and manufacturing will determine the number and types of players who enter, the set of branded biologics which can be targeted, and the overall revenue and profit potential of the market.

Establishment of a regulatory framework for approval within the U.S.

While biosimilar guidelines were approved in the EU in 2005, and a number of products are now on the market there, biosimilars are still relatively nonexistent in the single largest biologics market – the United States. To date, only one biosimilar – Sandoz’ Omnitrope – has been approved for use in the U.S. Omnitrope gained approval through the FDA’s 505(b)(2) abbreviated pathway for “follow-on protein products.” This pathway, however, has proved problematic.

Under the 505(b)(2) pathway, approval relies on the previous finding of safety and effectiveness for the compound on which the follow-on protein is based. This process is predicated upon the original compound and the follow-on protein being sufficiently similar to be considered the same.
product pharmaceutically. Given the complex nature of protein products and the manufacturing processes that produce them, it is no wonder that debate exists about how well this protocol applies to biologics – and therefore how much additional and original data must be provided to demonstrate equivalency.

In the case of Omnitrope, Sandoz relied on the data submitted for the prior approval of Pfizer’s Genotropin. In addition, they provided clinical data in support of Omnitrope’s pharmacokinetic, pharmacodynamic, physiochemical, and bioavailability similarity to Genotropin, as well as new pharmacology, toxicology, and safety data specific to Omnitrope. Although the documentation was not as extensive as would be required for a new drug, it still represented a significant investment of time and resources by Sandoz. Even with such extensive documentation, Omnitrope’s approval only came after years of consultation and a lawsuit between Sandoz and the FDA. Since its approval, no additional biosimilars have been submitted to the FDA, as the 505(b)(2) approval pathway is complex and limiting, and the FDA has yet to issue a biosimilar specific protocol for future applicants.

In order for the biosimilar market to emerge in the U.S., a new regulatory pathway for the approval of follow-on biologics will need to be developed and implemented. To that end, Congress has been working towards passing legislation to explicitly provide a process for FDA approval of biosimilars, though progress has been slow and contentious. Given the tone of the Obama administration and the emphasis on healthcare reform, it seems inevitable that a regulatory framework will be implemented in the near future. The only question that remains is how much it will favor, or impede, the approval of biosimilars.

Two of the key issues at stake are the market exclusivity period for branded biologics and the use of previous clinical data in biosimilar approval. In July 2009, the Senate health committee voted

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**Biosimilars Timeline**

**Key Events**

**EU**

**U.S.**

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
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</thead>
<tbody>
<tr>
<td>2005</td>
<td>October 2005: EMEA adopts biosimilar approval guidelines</td>
</tr>
<tr>
<td>2006</td>
<td>June 2006: FDA approves Omnitrope following lawsuit filed by Sandoz</td>
</tr>
<tr>
<td>2007</td>
<td>August 2007: Approval of Binocrit and Abseamed</td>
</tr>
<tr>
<td>2008</td>
<td>September 2008: Approval of Ratiograstim, Teragrastrim, and Biograstim</td>
</tr>
<tr>
<td>2009</td>
<td>May 2009: Senate health committee votes in favor of 12-year biotech exclusivity period</td>
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in favor of a 12-year biologic drug data exclusivity period which would grant biotech innovators a significant market exclusivity period to protect sales and profits. The ruling sides more heavily with manufacturers of name brand biotech drugs than it does with biosimilar developers, who themselves were lobbying for a 7-year window. This exclusivity period will have significant implications on portfolio planning and timing for biosimilar developers.

The second key issue is the extent to which prior clinical data can be used in support of a biosimilar application. As with the case of Omnitrope, the 505(b)(2) pathway allows for biosimilar applicants to rely partially on clinical safety and efficacy data from the prior approval of the target compound. Given the complex nature of the compounds in question and the manufacturing processes used to create them, many biotech developers argue that biosimilars are, in fact, not similar enough to their reference compounds for powerful tool for biosimilar developers to promote their uptake. Furthermore, some biotech developers have argued that their clinical data amounts to proprietary information and cannot be used by another party in support of their application. In the end, the amount of original clinical data required for biosimilar approval will determine the relative cost and necessary investment for biosimilar development, and the number of financially attractive biosimilar targets.

### Commercialization and Uptake

Prior to 1970, legislation prohibited pharmacists from substituting generic drugs for prescriptions written for brand name drugs. It wasn’t until the law was repealed and pharmacists were allowed to freely dispense generics that generic drugs gained popularity and the market grew. Now, much like the nascent generics market of 40 years ago, the biosimilars market stands to be significantly impacted by substitution policy.

Just as the complexity of biosimilars relative to generics has impacted their regulatory approval, it seems likely that this complexity could prevent, at least in the near term, pharmacy substitution as well. In Europe, several countries have already enacted laws banning the automatic substitution of biosimilars. In the U.K., the Medicines and Healthcare Products Regulatory Agency recommended in 2008 that all biologics be prescribed by their branded name rather than their non-proprietary name to prevent substitution at the pharmacy level. A similar policy in the U.S. would significantly reduce the uptake of biosimilars.

Third party payers and their strong influence on the U.S. pharmaceutical market will also significantly impact the uptake of biosimilars. Given the high cost of biologic therapies relative to small molecules, payers will wield considerable influence over biosimilar market dynamics. Given that biosimilars have the potential to significantly reduce therapeutic costs, it will be in the interest of payers to promote their use to drive costs down.

Even if automatic substitution is not permitted for biosimilars, their uptake could be driven by payers should they choose to provide formulary incentives for physicians and patients to switch to lower cost alternatives to branded biologics.

To date, however, no such incentives have been put in place to promote the use of Omnitrope over more expensive branded alternatives. In fact, branded hGH manufacturers responded to the Omnitrope threat by increasing rebate levels to dissuade payers from switching to the biosimilar. Still, payers remain a potentially powerful tool for biosimilar developers to promote their uptake.

Finally, the perception of the safety and quality of biosimilars by patients and prescribers will also significantly impact their commercial success. In the face of the biosimilar threat, many branded biologic manufacturers have argued that biosimilars may not be as safe or of the same quality as their branded counterparts. Although a biosimilar may be based on the same compound as a branded alternative, even minor differences in manufacturing processes could result in a final product with an unknown safety and toxicity profile. Given these concerns, it is uncertain how likely physicians will be to switch patients from an established biologic to a biosimilar for a branded product that already has years of demonstrated safety and efficacy, or even prescribe a biosimilar to a new patient without convincing safety data and further investment in safety trials. Anecdotal evidence has indicated that these concerns have hampered biosimilar uptake in Europe.
Until biosimilars establish a longer history as a viable alternative, it is likely that concerns over safety and quality relative to branded biologics will slow their uptake and serve as a focal point for branded manufacturers looking to protect their market position.

**Economic and technical feasibility of biosimilars for more complex molecules**

Much has been made of the large number of biologics with patents expiring by 2014 and the threat that biosimilars pose to them. While it is true that the expiry of these patents will expose billions of dollars of revenue to potential biosimilar competition, it is unclear how many of these compounds can be feasibly and cost-effectively duplicated by generics manufacturers.

To date, the few biosimilars that have been successful have targeted compounds such as somatropin and erythropoietin, with molecular weights in the 20kDa to 30kDa range. Many of the biologics with the greatest revenues, however, are significantly larger and more complex compounds such as monoclonal antibodies. These compounds will require even more sophisticated manufacturing processes and typically generate lower yields at relatively higher costs. The capital and expertise required to develop, scale up, and achieve yields competitive with experienced innovators, combined with the added uncertainty around gaining regulatory approval, may make entry of biosimilars in these markets less financially attractive.

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**Key Biologic Sales vs. Complexity**

**U.S. Sales, 2008**

![Molecular Mass (Daltons)](image)

**Implications for biosimilar developers**

Each of the factors outlined above will have wide-reaching implications for biosimilar developers, big pharma and traditional generics players alike, seeking to market products in the U.S. As the U.S. biosimilars market continues to evolve, developers will need to address a set of strategic challenges: if to play, where to play, and how to play.
“If to play” – the realistic assessment of whether or not a player has the assets and expertise to compete in the biosimilar market

Competing successfully in the U.S. market for biosimilars will require a broader set of skills than has historically resided in either the small molecules generic industry or with big pharma players. While numerous biosimilar developers have been able to develop a presence, these markets, especially in the developing world, have more relaxed regulatory and manufacturing standards. Although gaining FDA approval for a biosimilar in the U.S. likely will require less of an investment in clinical trials for the generation of safety and efficacy data than an NDA or BLA, it will still demand significantly more work than typical small molecule generic drugs.

The manufacturing resources and investment needed for a biosimilar will also greatly exceed that of a generic small molecule compound. While expressing the protein may be straightforward, scaling-up the fermentation process to generate competitive yields and developing formulations beyond oral delivery may be more challenging.

Finally, it is conceivable that the successful commercialization of biosimilars in the U.S. will require a field sales force outside of the traditional skills of the wholesale-driven generics industry. While big pharmaceutical companies have development, manufacturing, and sales force capabilities, their large-scale production, PCP salesforces, and cost structures may be inconsistent with the lower-scale production, specialty markets, and lean operations necessary to compete in the biosimilars market. As such, developers wishing to play in the U.S. market will need to perform a realistic internal assessment of their own assets, capabilities, and the role of partnerships to fill any gaps that they may have in their expertise.

“Where to play” – evaluation and planning to optimize the portfolio

Given the resources required to bring a biosimilar to market in the U.S., and the commercialization challenges that such products face, biosimilar developers will need to rigorously evaluate potential targets before investing in their development. While such portfolio planning is commonplace in both the biopharmaceutical and generics markets, the unique factors that biosimilars face will require a broader set of criteria, balancing market potential with the resources required to bring a specific target to market. In addition to standard assumptions for pricing, penetration, development costs, COGS, and launch expenses, companies will need to consider the complexity and clinical profile of the compound, its manufacturing process, yields, and safety issues, as all of these will impact both profitability and likely uptake.

For example, biopharmaceuticals for chronic conditions such as protein deficiencies would typically represent significant opportunities as patients take them for life. For biosimilars, however, the same logic may not necessarily hold true. While chronic conditions yield steady demand, they also have a higher barrier to switching than other conditions. In other words, patients are less likely to switch from a biologic that they’ve been taking for years to a biosimilar solely on the basis of price – especially if any questions about safety or efficacy exist. Thus, if the product is very complex and has a history of serious adverse effects, albeit in a very small portion of patients, the combination of potential low yields, high COGS, significant investment in safety trials, and specialty detailing costs may not support a price point that would incentivize switching. This in turn would make the product commercially unattractive. While chronic conditions may offer an opportunity for biosimilars once they are more established and are prescribed to newly diagnosed patients, uptake is likely to be slow with the rewards coming in the long-term.
Once developers overcome the development and regulatory hurdles, a number of commercial obstacles to achieving uptake will still remain. Biosimilar products in more established markets such as Europe have achieved limited success at displacing higher priced branded products. A combination of safety concerns, brand loyalty, and aggressive pricing strategies by branded manufacturers have contributed to their lack of traction in spite of their lower price. In order to maximize the market potential for biosimilars, each of these issues will need to be proactively addressed in the U.S. market.

The most significant lever to drive adoption of biosimilars is pricing. Although they will never be as cheap as generics relative to their branded counterparts, biosimilar manufacturers will need to optimize their pricing to capture market share. Given the higher per unit manufacturing costs and higher barriers to entry facing biosimilars, it has been observed that this pricing advantage is smaller than the discount that small molecule generics enjoy.

It has also been demonstrated that branded manufacturers will not simply maintain their pricing premium in full and cede these sales, rather they will respond with aggressive pricing and reduce their margin. In the case of Omnitrope, manufacturers of branded somatropin offered rebates for their product to counter the discounted price offered by Sandoz. Some analysts have cited Sandoz’ lack of a counter response to these rebates as a key factor in the product’s limited uptake.

Furthermore, biosimilar developers will need to proactively work with third party payers to promote the cost savings potential of their products. In the current cost-sensitive healthcare market in the U.S., these relationships have the potential to strongly influence the uptake of biosimilar products.

Biosimilar developers will also have to address the quality and safety concerns that currently stigmatize their products. In order to do so, biosimilar developers will need to invest in creating clinical data in support of their products’ safety and efficacy claims and then develop and institute more aggressive marketing campaigns to communicate this data to the marketplace. Such an effort will again require more assets and expertise than traditional generic drugs, but will be critical to maximizing biosimilar market potential.

### Projected Sales of Expiring Products

**Year of U.S. Patent Expiry**

<table>
<thead>
<tr>
<th>Year</th>
<th>Biologics</th>
<th>Conventional</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010</td>
<td>$35 (11%)</td>
<td>$31 (89%)</td>
<td>$66</td>
</tr>
<tr>
<td>2011</td>
<td>$42 (26%)</td>
<td>$46 (74%)</td>
<td>$88</td>
</tr>
<tr>
<td>2012</td>
<td>$11 (26%)</td>
<td>$31 (74%)</td>
<td>$42</td>
</tr>
<tr>
<td>2013</td>
<td>$20 (48%)</td>
<td>$24 (52%)</td>
<td>$44</td>
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<tr>
<td>2014</td>
<td>$22 (50%)</td>
<td>$22 (50%)</td>
<td>$44</td>
</tr>
<tr>
<td>2015</td>
<td>$16 (39%)</td>
<td>$25 (61%)</td>
<td>$41</td>
</tr>
</tbody>
</table>

*The potential market for biosimilars is projected to grow in the next 6 years as more biologics come off patent*
The U.S. Biosimilars Market

Implications for Biotech Innovators

Much as the rise of generics forced branded pharmaceutical manufacturers to develop new competitive strategies in response to eroding sales, biosimilars are poised to disrupt the competitive landscape of biologic innovators. Just as pharmaceutical companies responded with innovative new strategies some 40 years ago, a number of options exist for biotech companies to slow and minimize the impact of biosimilars on their revenue streams.

Much like the big pharma response to generics, biologic developers will have to adopt innovative portfolio planning and lifecycle management practices to maintain their revenue streams in response to this threat. For biotech companies that have been built around the development of innovative compounds and technologies, the role of Business Development and Commercial Operations will become more important and serve as vital partners towards maintaining and growing robust pipelines. By anticipating patent expiries and proactively working to identify innovative compounds or alliances to replace them, biologic developers can minimize the impact of biosimilars on their bottom line.

Marketing – effective messaging and pricing strategies to defend market position

Biosimilars do pose a threat to biologic developers in the U.S., but a number of perceived shortcomings with respect to safety and efficacy stand in their way. By exploiting these weaknesses in branding and marketing efforts, biologic developers can more effectively protect their market share from encroaching biosimilars. While biosimilars such as Omnitrope will be approved and enter the market with robust clinical data in support of their safety and efficacy, each will initially lack the proven history of therapeutic effectiveness that incumbent branded biologics have built. By gearing marketing efforts around promoting this proven track record and educating both patients and prescribers, biologic developers may more proactively prevent switching and substitution of their products with lower-priced biosimilars.

Although biosimilars promise to be lower-priced alternatives to their branded reference products, they will likely never achieve the same level of discount afforded to small molecule generics. As a consequence, biologic developers may be able to neutralize the biosimilars’ pricing advantage through discounted pricing of their own, rebate programs, or agreements with third party payers and larger purchasing organizations. Furthermore, by leveraging market research and competitive intelligence assets and observing the price elasticity of their products, biotech companies can use pricing as a tool to maximize the overall contribution of their products in the face of the biosimilar threat.

Product Evolution – maximizing the revenue contribution of innovative compounds

In addition to developing innovative commercialization strategies and messaging, biologic developers may also maximize a compound’s revenue potential by adopting the same lifecycle management strategies that small molecule developers have applied to their products.

One common strategy for extending the lifecycle of a compound going off patent is to seek approval for new formulations or indications. Because most biologic compounds are essentially “first-generation” products, there may be numerous opportunities to improve on these compounds through minor adjustments in formulation. An excellent example of this is Amgen’s development of Neulasta, a longer lasting, pegylated formulation of their G-CSF product, Neupogen.
By adding a polyethylene glycol unit to the filgrastim molecule, Amgen created a product that required only one injection per chemotherapy cycle as opposed to 10 or 11 injections for non-pegylated Neupogen. In this way, Amgen was able to improve upon an existing product, maximize its therapeutic potential by improving its convenience, and gain additional patent protection for the new formulation. By following Amgen’s example and focusing on developing improved second-generation formulations, biologic developers can more effectively extend the lifespan of a product and maximize its revenue impact.

Accepting that biosimilar competition is inevitable for their products, biologic developers may also maximize their potential by creating authorized biosimilars. By adopting the same strategy as authorized generics, biologic manufacturers may seek to manufacture and market identical products at reduced biosimilar prices. In this way, manufacturers may maintain the premium branding of the original compound while capturing a portion of the biosimilar market with a lower priced alternative.

Although they currently face significant obstacles and uncertainty, it is inevitable that biosimilars will soon have a substantial impact on the U.S. biologics market. The enormous potential of the market will likely be matched by significant complexity as biosimilar developers vie for their share, biotech innovators defend their territory, and the FDA and government grapple with regulatory issues to maximize the safety and benefit of innovative biosimilars to the healthcare system. In order to survive in this demanding market environment, it is important that the players look ahead and begin adjusting and developing new business strategies to capture these new opportunities and address potential threats.
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