Developing a Biosimilar Defense Strategy
By Sebastien Morisot, Matthew Cook, and Rohit Sood

The growing use of biologics across therapeutic areas, the patent expiration of highly profitable biological products, and increased cost-containment measures make the biosimilar space an attractive development area. The biosimilar market is expected to be worth $25 billion by 2020, which drives a growing number of companies to want to get involved (Figure 1).

To defend their position against the biosimilar threat, reference-product manufacturers are expected to take significant legal, regulatory, and marketing action. While reference manufacturers can leverage demonstrated real-world, long-term efficacy and safety data as key brand features, it is essential to develop a global, integrated biosimilar defense strategy. Developing a successful biosimilar defense strategy necessitates a careful assessment of the level of risk to the branded product’s business. Risk minimization strategies can then be developed and supported by the deployment of specific tactical tools at the local affiliate level.

Conduct a Risk Assessment
The legal, regulatory, and stakeholder policies surrounding biosimilars vary widely across regions. For a global manufacturer of branded biotechnology products, it is critical to delineate regions according to comparable levels of risk related to price tolerance, access, and uptake. Specifically, branded manufacturers should look to address the following questions to identify country-specific drivers and barriers for biosimilar uptake.

When and in Which Countries are Biosimilars Expected to Launch?

In the EU market, biosimilars are less restricted than in the US market, and 14 biosimilars have been approved since the European Medicines Agency (EMA) first established biosimilar guidelines. In the US, biosimilar products have been slow to emerge, but recent events are clearing the way. The Affordable Care Act (ACA) includes an abbreviated licensure pathway for biological products shown to be similar to an FDA-licensed biological reference product. The FDA has issued draft guidelines to clearly define a regulatory pathway for biosimilars and is actively communicating in an effort to encourage manufacturers to submit applications via this pathway rather than the traditional (but potentially easier-to-navigate) biologic license application (BLA) pathway.

In the past several years, a number of biosimilar-like products have been approved in the US. However, due to their approval prior to the inception of a biosimilar-specific pathway, they technically do not meet criteria for a biosimilar designation. As a result, biosimilar-like manufacturers are unable to advertise their biological and clinical equivalence to the reference product.

The most recent such approval was Teva’s proprietary version of Amgen’s filgrastim (Neupogen®), tbo-filgrastim, indicated to reduce the duration of severe neutropenia in patients with non-myeloid malignancies who are receiving cytotoxic chemotherapy. Teva
currently markets this product in Europe under the trade name Tevagrastim®, as biosimilar to Amgen’s Neupogen.

Tbo-filgrastim was filed in the US as a BLA, since a biosimilar approval pathway had not been established at the time of submission. But that has changed. Among the components of ACA, a subtitle called the Biologics Price Competition and Innovation Act of 2009 (BPCIA) amends the Public Health Service Act (PHSA) and establishes an abbreviated licensure pathway for biological products shown to be biosimilar to, or interchangeable with, an FDA-licensed biological reference product. Section 351(k) of the PHSA, added by the BPCIA, sets forth the requirements for an application for a proposed biosimilar product and an application for a supplement for a proposed interchangeable product.2

To fully assess when and where biosimilars will launch, companies will need to review clinical trial information for a given region and estimate study and regulatory timelines.

What is the Regulatory Pathway for Biosimilars Across Different Regions?

Reference product manufacturers need to be aware of the length of market exclusivity in various regions in order to plan accordingly for brands nearing key milestones.

In the EU, biosimilar developers are able to submit their applications eight years after the original reference product approval when data exclusivity expires. Reference product manufacturers get an additional two years of market exclusivity, and the EMA review would take an average of 17 to 20 months (based on retrospective analysis of time from filing to approval for 14 biosimilars). This means that EU biosimilar products can be launched approximately 11 years after the launch of the reference product.

The US market exclusivity period is 12 years. Biosimilar manufacturers can then ready their launch once the 12-year period has lapsed (presuming there are no patent issues). Debate continues over whether to reduce exclusivity requirements from 12 years to 7 years, per a deficit reduction plan announced in September 2011. Uncertainty remains over exclusivity requirements in the US. In addition, extension of patent life—such as that seen for Amgen’s

**FIGURE 1A: Biosimilar Market Opportunity**

Value of Biologics Losing Patent Protection

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<thead>
<tr>
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<th>Revenue ($)</th>
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<tbody>
<tr>
<td>Current</td>
<td>11.8</td>
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<tr>
<td>Near Term (&lt;6 years)</td>
<td>53.4</td>
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<tr>
<td>Long Term (6-10 years)</td>
<td>62.7</td>
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Source: Campbell Alliance Analysis, 2013; EvaluatePharma. Accessed May 2013
Enbrel®—creates major hurdles for biosimilar manufacturers.

Unlike most generics, biosimilars do differ from their reference products due to inherent differences in cell lines, raw materials, equipment used, processes, and process controls. Molecular variations can ultimately lead to increased or decreased potency or immunogenicity—and therefore to safety issues. Consequently, the FDA requires that biosimilars be extensively characterized to reduce or eliminate uncertainty in similarity to the reference product.

The EMA has created and approved a set of overarching guidelines for biosimilars, which filter into product-level requirements addressing quality issues and clinical and non-clinical issues. To date, the EMA has issued seven product-class-specific guidelines, including the recently finalized guidance for monoclonal antibody biosimilars.

While lacking the granularity of EU guidelines at the product level, the FDA has emphasized a “totality of the evidence” approach in reviewing all information, reducing residual uncertainty when comparing a biosimilar with its reference product. Manufacturers must combine multiple complementary methods with strategies that allow for a
“fingerprint-like” identification of similar patterns in different products. Materials in support of a biosimilar approval must include detailed analytical testing, clinical immunogenicity evaluation, animal studies, and human clinical trials. Given the complexity of biologics, there will be no “one-size-fits-all” assessment. Instead, the FDA will evaluate the extent to which each applicant successfully integrates all of the above information to determine if the biosimilarity standard is met. The bioequivalence exercise follows a step-wise, increasingly targeted process, starting with broad physico-chemical analyses, leading to a limited number of small-scale clinical studies.

The FDA has been actively working to encourage manufacturers to submit their applications through the biosimilar-specific pathway. More than 30 biosimilar meetings were conducted by the FDA regarding biosimilar clinical development programs; to date, however, no company has submitted a biosimilar marketing application. Their reluctance may stem from the fact that the 351(k) pathway requires that biosimilar manufacturers disclose their entire product dossier to the reference product manufacturer at the time of filing. Meanwhile, the reference product manufacturer would be required to provide its manufacturing processes to the FDA, handing the regulatory body trade secrets from both organizations. Another reason manufacturers may be reluctant to pursue the biosimilar pathway is that they are simply concentrating on the likelihood of approval and view the traditional BLA as less risky because of their familiarity with the process and the pathway’s established track record of success with the FDA. Utilizing the unfamiliar, untested 351(k) biosimilar pathway presents the risk of a delayed approval or an outright refusal by the FDA.

Manufacturers may also see the traditional BLA pathway as a safer route to approval as they can avoid the bioequivalence studies required by the biosimilar pathway. This may set the manufacturers up for a much more challenging marketing process as they will not be able to leverage any comparative data with the reference product. This does not necessarily mean the new market entrant will be any less of a threat for the reference product manufacturer.

How Does/Will the Country Define Interchangeability, and What is the Policy on Automatic Substitution?

In the EU, decisions regarding interchangeability are decided by the individual countries. Due to concerns around the traceability of adverse events, almost all EU country regulatory bodies have established rules against automatic substitution. In France, automatic biologic substitution is prohibited. In Germany, branded products cannot be automatically substituted, but biosimilar-to-biosimilar substitution is permitted (within specific groups). Italy, Spain, and the UK have established guidance and official lists of non-substitutable medicines that include all biologics.

In the US, legislation regarding biosimilars varies from state to state and is constantly evolving. Virginia, Utah, and North Dakota have passed laws that permit pharmacists to dispense a biosimilar in place of a prescribed biological product only if that biosimilar meets the higher safety standards for “interchangeability.” Meanwhile, states like Arizona, Maryland, Mississippi, and Washington have rejected similar laws. Numerous other states have legislation that is expected to be considered.

What are payer, physician, and patient perceptions of biosimilars in the high-priority countries?

Although the price reduction for biosimilars will be nowhere near what is currently seen for generics (i.e., around 90%),
biosimilars hold appeal for the three primary stakeholders: payers, physicians, and patients.

Payers are carefully monitoring the budget impact of costly biologics especially in high-scrutiny areas such as inflammation or oncology. The addition of cheaper biologics in the form of biosimilars to their formularies therefore represents a compelling alternative to historically costly treatments.

Physicians’ awareness of biosimilars is steadily increasing. However, while they are getting increasingly comfortable with the idea of biosimilars, physicians will demand tolerability and immunogenicity data and long-term safety data supporting clinical equivalence before making prescribing decisions favorable to biosimilars rather than reference products.

Physicians are likely to be more open to using biosimilars (or biosimilar-like versions) of smaller proteins or more “commoditized” products such as supportive care agents like erythropoietin and granulocyte colony-stimulating factor. More complex biosimilars, including proteins such as interferons or even monoclonal antibodies, will have more variations when compared with their originators, which may deter physicians from using them. As physicians can also be creatures of habit, they are likely to adopt a biosimilar product with dosage and administration identical to the reference product.

While patients may not have as much weight as payers and physicians in driving the uptake of biosimilars, out-of-pocket payments for both non-insured and insured patients will likely be reduced if switching to a biosimilar-based treatment.

Develop Strategies

Once a foundational understanding of how the biosimilar landscape will operate in each country has been established, it is then possible to cluster different markets that represent similar levels of risk. Similar defensive strategies can then be developed and pursued across similar regions. These strategies can take a number of different forms.

Positioning and Messaging

Manufacturers operating in competitive markets are used to differentiating their brands with efficacy, safety, and other clinical data. New biosimilar market entrants, however, will potentially broaden the discussion to include increased emphasis on cost differentiation.

Reference-product manufacturers will need to look beyond just product messaging. For example, manufacturers may be able to craft a meaningful message around manufacturing capabilities, touting product quality and availability; brand-product manufacturers can also develop competitive messaging around the medical education and patient engagement and support programs they are able to provide as a result of their long history with the product and the disease state.

The timing with which the sales force shifts from promotional messages to competitive messages is a critical decision. This is particularly the case in situations where the biosimilar may be the first real competitor to the branded product. Does it make sense to wait for the biosimilar to launch? Or would it be better to try to prepare the market for the arrival of the biosimilar product with preemptive competitive messaging? Subsequently, the manufacturer of the brand product will need to determine to what extent it will be necessary to invest in additional sales resources to maintain share of voice for the branded product.

Account Management and Payer Segmentation

As biosimilar entries are nearing, global reference-product manufacturers must ensure that they have developed
appropriate contracting capabilities to maintain preferred positioning on formularies.

In particular, it is critical to develop a detailed account segmentation map to understand different customer segments and sub-segments (hospital inpatient vs. outpatient settings, clinics, etc.) as well as their pricing sensitivities and key considerations when purchasing biologics (e.g., do they favor acquisition costs or cost recovery?). Proper identification of key accounts will allow for focused efforts against a new entrant. For example, 340b hospitals eligible for government pricing are likely to switch to a lower-cost biosimilar (even with marginal price difference) to maximize savings.

In some instances, a successful defensive strategy may require securing of specific accounts through creative contracting terms. Risk-sharing, cost-sharing, and product replacement approaches may appeal to particular accounts and help differentiate from biosimilar competitors.

Without contracting plans in place, a company runs the risk of being taken by surprise by a sudden price change in the market. In these instances, payers allow a limited time period for competing products to respond to the change, so proactive companies should have a cohesive, well-thought-out plan ready to put into action, should it be appropriate.

**Opinion Leader Management and Engagement**

Physician advocacy can be instrumental in supporting a brand. Product champions and influential key opinion leaders who are experienced with a reference product can communicate the value and highlight key differences between branded and biosimilar products. In an effort to maintain continuous engagement of the physician community, a reference-product manufacturer should also consider exploring a clinical trial program involving authoritative centers.

Providing value-added services such as patient assistance programs will aid in the effort to defend a brand. The goal is to maintain sufficient brand loyalty, where a cost difference is not going to be enough for a payer to make an access change and/or a physician to make a prescription change.

**Develop Global Biosimilar Defense Toolkits**

Once a defensive strategy has been determined for the brand, it will then be necessary to identify tactics that will support execution of the strategy in each of the affiliate clusters. Tactics will need to be customizable to local needs and specific market environments. After specific and practical tactics have been identified, it will then be necessary to define priorities, timelines, costs, and responsibilities associated with each tactic.

Various global biosimilar defense toolkits can be developed. A clinical data kit can support a country sales rep to better communicate safety and efficacy data. This would address the messaging piece of the defensive strategy. For example, one of the clinical messages that a branded product has that a biosimilar does not is real-world safety data. The years the brand product has been used by physicians should count for something in the minds of stakeholders. While the clinical trial data may show that the biosimilar product is just as efficacious and just as safe, the brand product could have a decade of real-world evidence of its safety and efficacy behind it.

An objection handler kit can also be developed to help the field force address objections when comparing the brand with biosimilars.

A contract and rebate guide can be developed to provide guidance for each affiliate cluster in terms of the contracting and rebating strategy that will be used. This will address the account-level segmentation piece of the defensive strategy. Such a guide can provide...
account managers with direction regarding how various payer stakeholders are potentially going to react to a biosimilar hitting the market and how they can most effectively contract and work with each individual account.

A physician management tool can be developed to help form a global network of key opinion leaders and optimize relationships with them. This will address the opinion leader management and engagement piece of the defensive strategy. It is important to ensure the people who have historically spoken and advocated for the brand product continue to emphasize the brand name as opposed to the generic name for the product.

**Conclusion**

The growing number of biologics set to undergo patent expiry and increased cost pressure create a favorable environment for biosimilar development. In 2012, EU biosimilar sales represented less than 10% of total biological sales; however, uptake of biosimilars has varied considerably across Europe, with the most successful product launches occurring in the UK and Germany, where payer/government influence over utilization is the strongest. For example, in Germany in 2011, erythropoietin biosimilars represented 14% of total sales in the category.

In the US, it remains to be seen whether biosimilars will truly make a dent in an originator’s market share. Physician reluctance, FDA guidance, and lack of clarity regarding development and interchangeability contribute to the overall sense of uncertainty, which may have contributed to some companies prematurely stopping biosimilar development programs (e.g., Teva and rituximab). Many unknowns surround biosimilars, and as a result, it is possible to influence key stakeholders or leverage insecurity in the marketplace. The recent clinical issues faced by Affymax’s Omontys® that led to a product recall illustrate the latent uncertainty with alternatives to well-established brands such as Epogen®. While Omontys is not an Epogen biosimilar, this event will certainly trigger more scrutiny from physicians considering the switch from a well-characterized and understood molecule.

What is in question is whether biosimilars will, over time, completely overtake branded equivalents (i.e., typical generics) or whether the biosimilar market is set to operate differently and only serve those for whom cost is a key driver of product choice.

Nonetheless, reference-product manufacturers can no longer ignore the threat posed by biosimilars and the likely-to-increase support that biosimilars currently get from regulatory authorities and health insurance plans. An understanding of the approval and reimbursement pathway and how stakeholders will react to biosimilars is critical to forming strong defensive strategies and tactics and ensuring the continued value of branded biologics.
References:

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