The Business of Biosimilars: The Key Challenges of Pharma Forecasting

By Stephen Lamb and Art Cook
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When biosimilars launch, the dynamics that will play out in a given therapy area or geography are highly uncertain. Given that biosimilars represent an entirely new product category—one with just a handful of early examples to date—the challenges to the forecaster are unique and formidable. The challenges apply equally to those tasked with forecasting biosimilar uptake or originator erosion.

There are two key considerations (among many others) that make projecting biosimilar uptake difficult and significantly more complex than projecting the uptake of a standard small-molecule generic. The first is their “similar” nature. In contrast to generic small-molecule pharmaceuticals, biosimilars are not exact chemical copies of the originator; rather, they are “similar” to the originator product. The second consideration that makes projecting biosimilar uptake different from that of a typical generic is the level of price differentiation that biosimilars will offer. While generic small molecules often cost just pennies on the dollar vs. their originator reference products, the discounts offered by biosimilar manufacturers are expected to be considerably more modest.

If we look at a typical patient-based forecast funnel—the high-level flow from market opportunity to realized revenue—biosimilars have the potential to affect the forecast at each point. All potential effects must be considered by the diligent forecaster when projecting the dynamics of biosimilars in the market.

Figure 1: The patient-based forecast funnel
Diagnosed Patient Pool

The top portion of the forecast funnel is the least likely to see a significant disruption due to biosimilar entry, although some impact is theoretically possible. If we consider biosimilars as offering a less expensive alternative to existing therapies, there’s no compelling reason that the diagnosed patient pool would grow with biosimilar introduction. One possible exception might be if a biosimilar manufacturer were to undertake a disease awareness campaign as part of its promotional activities. If this were to occur, the diagnosed pool might increase, but it’s reasonable to assume that biosimilars will not influence the number of diagnosed patients with a given condition.

Treated Patient Pool

This portion of the funnel also is not likely to change drastically following the introduction of biosimilars. However, if price barriers to treatment become less of a concern with the (presumably) less expensive biosimilar, the possibility of the drug treatment rate increasing does exist. This dynamic would be linked to reimbursement coverage or wealth levels of various markets, but an increase in treatment rates is reasonable to expect in some cases. There is some evidence of this to date, with the most well-known example being that of biosimilar filgrastim in the U.K. The availability of biosimilar filgrastim at a significant cost savings vs. branded Neupogen grew the market and expanded patient access to the therapy. This dynamic was primarily driven by procurement tenders where cost savings led to the tender winner’s (biosimilar filgrastim) inclusion in first-line guidelines at many hospitals. The limited safety concerns around filgrastim biosimilars also may have helped contribute to its overall growth. Overall, daily volume usage of filgrastim in the U.K. has grown 40% since biosimilars became available.

Product Share and Adoption

This is the most uncertain and variable part of the forecast funnel as it relates to biosimilar uptake and subsequent originator erosion. To appreciate the complexities of understanding (and forecasting) share dynamics, we need only look at the number of forces (both drivers and barriers) influencing uptake across stakeholders. While the framework in figure 2 is most applicable to the U.S. market, select components also are applicable to markets outside of the U.S.
The considerations in figure 2 demonstrate the wide array of factors at play. For a forecaster to project biosimilar uptake or erosion, all drivers and barriers of adoption must be considered, and a future-state scenario (or scenarios) should be defined. Once assumptions are made, the market can be mapped along the various dimensions in figure 2 to understand how likely a market is to experience high or low uptake, and what the key drivers of uptake are likely to be. From here, a detailed modeling exercise can be carried out, and analytical rigor tailored to the expected importance of various dynamics can be added (new vs. continuing patient switching, provider-by-provider contracting expectations, payer-by-payer policy expectations, etc.).

In exploring early biosimilar experiences in the U.S., different levels of uptake can be observed. The relative success vs. failure of biosimilars across different markets can be traced back to the drivers outlined in figure 2. It’s important to note, and will become clear in the following examples, that payer influence has proven to be the dominant variable influencing biosimilar uptake to date in the U.S. market. While the impact of patients, providers and regulators is real—and critical to consider when forecasting biosimilars—these stakeholders have not yet been as important in dictating uptake rates as have been payers.

### Figure 2: Drivers and barriers of biosimilar adoption by stakeholder

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<th>Drivers</th>
<th>Adoption</th>
<th>Barriers</th>
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<td>Providers</td>
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<td>Liability concerns</td>
<td>Supply concerns</td>
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<td>Brand loyalty</td>
<td>Lack of trust in safety data</td>
<td>Reference pricing</td>
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<td>Originator rebates and contracting</td>
<td>Lack of trust in manufacturing</td>
<td>Formulary guidelines</td>
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<td>System cost pressures</td>
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<td>Patients</td>
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<tr>
<td>Loss of support services</td>
<td>Unaware of difference vs. branded</td>
<td>Biosimilar value-add programs</td>
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<td>Brand loyalty</td>
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<td>Growing acceptance</td>
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<td>Lack of trust</td>
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<td>DTC marketing</td>
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<td>Lower co-pay</td>
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<td>Better delivery devices</td>
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<td>Physician prescribing</td>
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<td>Payers</td>
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<td>Reluctance to switch initiated patients</td>
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<tr>
<td>Patient or physician resistance</td>
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<td>Originator discounting, rebating, contracting</td>
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<tr>
<td>Regulatory</td>
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<tr>
<td>Naming complexities</td>
<td>Single-payer/government policies</td>
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<tr>
<td>No extrapolation or interchangeability</td>
<td>Extrapolation/interchangeability</td>
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<tr>
<td>Substitution restrictions</td>
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<td></td>
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<tr>
<td>340B discount exemptions</td>
<td>Quotas/shared savings(single payer)</td>
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Looking at the first biosimilar launched in the U.S., Sandoz’s/Novartis’ Zarxio (a biosimilar of Amgen’s Neupogen/filgrastim), modest initial uptake is observed, perhaps driven by several factors. Although Zarxio launched at a 15% list price discount to Neupogen, Sandoz initially didn’t have many contracts in place to drive payer preference. Furthermore, some payers indicated that they were waiting for the biosimilar pegfilgrastim (Neulasta) before attempting to control the joint filgrastim and pegfilgrastim market. On the provider side, promotional efforts were perceived as restrained. According to one survey by DRG, a large proportion of oncologists initially believed that they didn’t have access to Zarxio, and the majority had not seen a sales representative from Sandoz or Novartis in the post-launch period.

After a slow initial few months, Zarxio’s performance improved meaningfully, with its share of the U.S. filgrastim market growing to around 30% by the end of the first quarter of 2018. Commercial pharmacy benefit managers have begun replacing Neupogen with Zarxio on their formularies (spurring uptake), and physicians have cited additional promotional support from Sandoz. Beyond this, however, another key to Zarxio’s success has been its penetration within the institutional channel where 80% of its prescription volume has been generated, according to Symphony Health Solutions data accessed via Bloomberg. This channel dynamic presents yet another potential complication for a forecaster to contend with: a need to understand relative channel size and relative biosimilar penetration within each.

SHARE OF U.S. FILGRASTIM MARKET (PERCENTAGE)

![Graph showing share of U.S. filgrastim market with data from Symphony Health Solutions accessed from Bloomberg in May 2018]

Source: Symphony Health Solutions data accessed from Bloomberg in May 2018

Figure 3: Share of U.S. filgrastim market

The next two biosimilars to launch in the U.S. (Pfizer’s Inflectra, a biosimilar of Janssen’s Remicade, and Lilly/Boehringer Ingelheim’s Basalgar, a biosimilar of Sanofi’s Lantus) launched at the end of 2016. However, in their first year on the market, the two have achieved very different penetration levels, offering interesting case studies.
In the case of Remicade, Janssen/Johnson & Johnson’s aggressive (and preemptive) defense through rebating and contracting strategies played a big role in its protection from Inflectra erosion. Long-term contracts (including portfolio contracting) with payers for preferential use resulted in minimal pressure on physicians to substitute Inflectra. Further, while Inflectra was launched at a 15% list-price discount vs. Remicade, its average selling price was approximately 22% higher (per CMS pricing information). This pricing approach presumably didn’t provide sufficient savings to payers or cost recovery to providers to drive conversion.
Inflectra also faced challenges in the regulatory domain. Inflectra came to market with a carve-out label (approval in only seven of eight Remicade indications), casting doubt on its equivalence to Remicade. Additionally, Inflectra did not receive an interchangeability designation from the FDA. Janssen leveraged these two facts in its defensive messaging strategies. The FDA also faulted the Celltrion site where Inflectra is manufactured for many shortcomings, including its failure to quickly investigate reports of particulate-contaminated vials and customer complaints of vial stopper issues (presumably also casting doubt on Inflectra’s quality).

Facing these headwinds, Inflectra has struggled in the U.S., with its limited uptake heavily concentrated in highly integrated health systems, including the U.S. Department of Veterans Affairs.

Looking at biosimilar entry in the insulin market illustrates a case where different market conditions have led to a very different result for Basaglar, which has had relatively high penetration vs. the Inflectra/Remicade example. The relative success of Basaglar can be attributed to the nature of the insulin market itself. Given the high cost to payers of diabetes, it’s a heavily controlled market. This fact manifests itself in payers’ higher willingness to impose controls and providers’ greater sensitivity to insurance coverage—both points that would tend to work in favor of a cost-reducing biosimilar. Further, provider sensitivity to switching and equivalence in the insulin market is significantly lower than in the anti-TNF market (again, factors that make the market more favorable to biosimilars).

In reviewing the dynamics at play in the Zarxio, Inflectra and Basaglar examples, the complexity and variability in drivers become abundantly clear, but the complexity hasn’t yet fully manifested. Over time, the level of biosimilar comfort and acceptance of physicians, payers and patients is also likely to increase, thus shifting the drivers and barriers to biosimilar adoption as detailed in figure 2. This offers an additional wrinkle for a forecaster to consider when thinking through potential biosimilar uptake. What has played out in the early days of biosimilars in the U.S. may not be a great analog five years from now when physician acceptance (as well as that of patients and payers) has evolved.
Fulfillment, Duration and Compliance

This is an area of the forecast funnel that might see some limited impact due to biosimilar availability. If we assume that biosimilars are essentially equivalent in efficacy and outcomes to their originator counterparts, there’s no compelling reason for a change to occur with these variables. The opportunity for impact becomes more likely if patient sensitivity to cost is a major element. In this case, if a biosimilar manufacturer were to offer significant patient out-of-pocket cost assistance (above and beyond what’s offered by the originator), then improved fulfillment, duration and compliance could materialize. It’s important to note that this would only be at play in markets such as the U.S. where a single-payer system doesn’t exist, and patients are expected to share in costs and overcome administrative hurdles to get on therapy. On the opposite end of the spectrum, it’s also possible that biosimilars might hurt fulfillment, duration and compliance. Conditions that might precipitate such a non-intuitive outcome would be specific: Payers would need to mandate biosimilar use (or a step-through), and the biosimilar manufacturers would need to offer inferior assistance to existing originator programs. In such a case, a patient who may have previously had originator out-of-pocket cost support might now be facing a situation with the same co-pay but no assistance—a direct hit to fulfillment and compliance. The likelihood of this can be debated, but a real possibility does exist.

The Future of Biosimilar Forecasting

The task of forecasting biosimilar uptake or erosion is challenging. The difficulties faced by a forecaster in understanding the dynamics at play in her market, and how these dynamics are likely to translate to effects at various points in the forecast funnel, are significant. The additional consideration that the dynamics at play (and their effects) may change as stakeholder acceptance of biosimilars grows only further complicates this task. Only with careful and holistic consideration of potential influencers, and a rigorous, data-derived analysis of the effects, can a reasonable approximation of uptake and erosion be made.
Looking to Europe

Biosimilar Uptake in Europe (Percentage of Market Volume)

**Neupogen (filgrastim)**

- Germany
- U.K.
- France
- Spain
- Italy

**Epogen (epoetin alfa)**

- Germany
- U.K.
- France
- Spain
- Italy

**HGH (somatropin)**

- Germany
- U.K.
- France
- Spain
- Italy

Figure 6: Biosimilar share of select EU5 markets
To briefly touch on EU5 markets, a high level of variability has also been observed to date. While many physician and patient drivers and barriers in Europe mirror those of the U.S., the varying degree of cost controls, quota systems, tenders and value-based pricing schemes has led to differential uptake across markets.

The biosimilar filgrastim offered compelling cost savings across EU5 markets, which has helped it achieve strong penetration in all EU5 markets. The biosimilar’s best penetration has been achieved in the U.K. and France—both driven by hospital tender wins. Strong uptake was also observed in Germany due to the quota system in place.

The epoetin alfa case shows a striking difference in uptake in Germany vs. other EU5 markets. Here again it was quotas driving uptake, along with education sessions and government encouragement to physicians to foster uptake. Uptake was muted in the U.K. due to originator cost reductions, and in France uptake was lower due to safety concerns. Spain is the only other EU5 market with a meaningful level of biosimilar epoetin alfa penetration, driven by payer pressures for new patients to be initiated on the biosimilar product.

Finally, in the human growth hormone market, the biosimilar somatropin has seen extremely limited uptake across the entire EU5. In this case, the biosimilar offered a delayed efficacy onset and minimal cost difference vs. the originator reference product—both elements that hindered uptake.

Even in centralized markets often considered to be less complex than the U.S. market, we can see in figure 6 that high variability is still the norm. As in the U.S., the challenge faced by a forecaster in approximating biosimilar uptake or erosion is again not trivial. Only with careful consideration of all relevant dynamics and an understanding of likely tender outcomes can we strive to reasonably approximate uptake.
About the Authors

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