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Biosimilars: Strategic considerations for interchangeability

The future timing, magnitude, and impact of the anticipated biosimilar wave continue to be in flux. Major biopharmaceutical manufacturers (e.g., Pfizer, Novartis, Eli Lilly), generics powerhouses (e.g., Teva, Mylan), collaborations across these two types (e.g., Amgen and Actavis), and even non-traditional players (e.g., Samsung, in partnership with Biogen Idec and Merck) have announced their positions and made strategic investments in biosimilars. However, deciding *how* to engage and win depends on yet unsettled regulatory parameters.

A particular area of uncertainty is interchangeability—a designation which could allow pharmacists to substitute biosimilar products meeting this standard for reference products, potentially without involving prescribers. At first glance, this could be viewed as a powerful lever for a manufacturer of a biosimilar to mitigate spending on marketing and sales activities and gain share. An interchangeability designation may also represent a step up from biosimilarity and provide physicians and patients with additional confidence in the product, as has happened with AB-rated small molecule generics in the US.

In the EU and the US, the regulatory requirements for an interchangeability designation are not yet settled.[1] However, if interchangeability were a viable option for manufacturers, would it *always* make sense to seek it, especially as it may be more expensive, time-consuming, and difficult to do so? For example, in the US, biosimilarity and interchangeability could be sequential Food and Drug Administration (FDA) decisions; pursuing interchangeability later in the process could extend the approval period and require a switching study.[2] In certain situations, a manufacturer may find it more beneficial to position a new product as a “me too” biologic brand or a “biobetter”. The optimal regulatory strategy will be defined by product and manufacturer characteristics, which we explore here. Because of the diversity and complexity of these characteristics, there will not be a single, optimal strategy regarding pursuit of interchangeability for all biosimilars. Instead, we expect a continuum of strategies to emerge in the marketplace.

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[1] See, for example, “Guidance for Industry on Biosimilars: Q & As Regarding Implementation of the BPCI Act of 2009: Questions and Answers Part I,” U.S. Food and Drug Administration, February 2012, p.11; “Germany: ‘EU's most favourable market for biosimilars’,” *PharmaTimes*, May 30, 2013.

[2] “Biosimilar Price Competition and Innovation Act – Discussions on the Biosimilar Pathway,” *Policy and Medicine*, September 11, 2012.

Product category characteristics

In addition to the expected ease or difficulty of securing an interchangeability designation, the attractiveness of this designation is affected by five product category characteristics: mode of dispensing, disease state, competitive dynamics, manufacturing challenge, and payer economics.

Mode of dispensing

A key first consideration is whether there is a point of intervention, between where a physician prescribes a product and a patient is treated with it, such that an interchangeable variant could be substituted. If such a point exists, an interchangeability designation may be valuable in overcoming barriers in the reference-to-biosimilar substitution. These barriers may include the following:

- physician hesitancy to prescribe the biosimilar over a familiar choice;
- patient hesitancy to request, or lack of familiarity with, a less expensive biosimilar;
- payer hesitancy to steer utilization toward the biosimilar, e.g., due to incumbent contracts; and
- existence of proprietary differentiating features, such as delivery devices.

If such a point of intervention does not exist, e.g., for an office-administered therapy, the mere presence of an interchangeability designation will not offer direct, structural advantages in driving either access improvements or share gains. For office-administered therapies, a physician often serves as a *de facto* arbiter of whether to substitute a biosimilar for a reference product. An official interchangeability designation may help sway the decision, but brand-like marketing efforts may be more effective.

Disease state

If a disease state is severe, interchangeability may provide an initial imprimatur of quality to physicians and patients. This may increase confidence in a biosimilar and generate incremental utilization. A chronic disease state, such as rheumatoid arthritis, provides fewer opportunities to generate new patient starts for the biosimilar. In this situation, interchangeability could confer an important benefit, unlocking cohorts of patients who otherwise would not be available for capture, given physician tendencies to keep continuing patients on existing therapies.

In less severe and/or more acute disease states, interchangeability may not be as critical or valuable. A further signal of quality may not be as essential for physicians treating patients with less severe conditions. In these situations, a physician may prescribe a biosimilar without as much hesitation, and traditional marketing efforts may be more effective than an interchangeability designation. In acute disease states, frequent patient turnover means there is less value from leveraging interchangeability to switch a particular patient and more opportunities to capture new patient starts in other ways.

Competitive dynamics

If a market is significantly concentrated and/or characterized by a high degree of loyalty to a reference brand, a first-to-market interchangeability designation may be a cost-effective way to capture share. In a fragmented market, where physicians, patients, and payers are already used to choosing from among multiple options (branded or generic), interchangeability may help convert only a relatively smaller segment. In either case, however, share gains would need to be defended against other interchangeable and potentially lower-priced options; in fact, interchangeability could make it easier for future biosimilars to capture the share secured by a first-to-market biosimilar.

Manufacturing challenge

All else being equal, a product that is easier to manufacture is likely to attract more biosimilar entrants, including ones pursuing interchangeability, than one that is relatively difficult to manufacture. If many biosimilars enter the market, price will become the key lever, and brand-like strategies will not be as effective. One or more competitors may seek interchangeability, and this approach may then become a cost of entry for future participants. A lower number of biosimilar entrants, however, is likely to result in less dramatic price erosion, potentially making a brand-like strategy more attractive.

Payer economics

Payers may not be inclined to steer utilization to a particular biosimilar for economic reasons, such as the installed base of rebates on a branded product. When looking at savings opportunities, a payer would consider these rebates versus anticipated incremental discounts (assuming some ability to drive share to the biosimilar). When the calculus favors the former, a payer may take a hands-off management approach, and the biosimilar manufacturer may need to consider alternate levers such as interchangeability. When it favors the latter, and a payer is willing and able to drive patients to a biosimilar option, interchangeability becomes relatively less valuable.

Three examples: Herceptin, Humira, and Lantus

These product category characteristics can be applied to three high-profile and high-value biologics, Herceptin (trastuzumab), Humira (adalimumab), and Lantus (glargine), each of which has biosimilar entrants on the horizon. As Herceptin is physician-administered, the first order benefit of pharmacy substitution conferred by interchangeability does not apply, although interchangeability may help physicians gain confidence in a biosimilar trastuzumab and overcome potential payer reluctance to intervene. Interchangeability may benefit adalimumab biosimilars as an avenue to drive patient switches at the pharmacy, although physicians and patients are likely to expect biosimilar manufacturers to match AbbVie's service offerings. The market uptake benefit of interchangeability may be greatest for the first glargine biosimilar that secures the designation, prices effectively, and is able to capture a large share of Sanofi's installed patient base. Manufacturers of these biosimilars would need to examine their own willingness, ability, and returns from sales and marketing efforts relative to prospects for, and returns from, securing interchangeability designations.

	Herceptin (trastuzumab)	**Humira (adalimumab)**	**Lantus (glargine)**
Mode of dispensing	Physician-dispensed	Pharmacy-dispensed	Pharmacy-dispensed
Disease state	Severe and chronic	Less severe, although chronic	Less severe, although chronic
Competitive dynamics	Concentrated (high profile brand), with high brand loyalty	Fragmented; differentiation on service elements	Concentrated (high profile brand), with high brand loyalty
Manufacturing challenge	Highly complex	Highly complex	Less complex
Payer economics	Lower anticipated discounts	Higher anticipated discounts	Higher anticipated discounts
Summation—Would interchangeability help?	**Given mode of dispensing, only benefit is if physicians accept an interchangeability designation as a critical imprimatur of quality**	**Potentially a way to capture installed base of chronic patients using Humira; support programs may be required**	**For the first entrant, can be a key lever to convert a large cohort of patients prior to launch of competitor biosimilars**

Green—interchangeability more beneficial
Red—interchangeability less beneficial

Manufacturer characteristics

Not all biosimilar manufacturers are capable of pursuing “high-touch” avenues. Manufacturer characteristics also influence the attractiveness of pursuing interchangeability. An interchangeability designation is, essentially, a generics-like feature that diminishes the importance of traditional, brand-like efforts and levers available to a manufacturer. It may help override deficiencies in (or absence of) existing relationships with physicians, patients, and payers. It may also help some, especially new-to-market, manufacturers overcome limitations in commercialization experience and resources.

Some manufacturers may neither need nor want interchangeability. Experienced and well-resourced companies such as Pfizer or GSK may wish to retain control and flexibility to communicate clinical or other differentiating (“biobetter”) attributes, support a broader portfolio of products in the therapy area, maintain pricing discipline, and offer physician and patient support services. Traditional generics manufacturers such as Ranbaxy or Dr. Reddy’s, with prior experience launching biosimilars in BRIC or other emerging markets, may have diverging viewpoints, objectives, and assets in place. Hybrid manufacturers such as Teva or Novartis/Sandoz, or alliances between companies (e.g., Amgen and Actavis, Merck and Samsung Bioepis) may fall in between, or have different perspectives.

Summation: Interchangeability and heterogeneous strategies

Pursuing an interchangeability designation may be expensive, time-consuming, and difficult to achieve. Furthermore, there are important strategic considerations that argue against indiscriminately choosing to pursue this designation, particularly for certain biologic product categories and for experienced and well-resourced branded manufacturers.

The wide range of biologic product categories and manufacturers makes it difficult to assess just how broadly interchangeability will be pursued in the near future, and how reference product manufacturers will need to respond. The underlying complexity of biologics, including administration requirements and physician and patient support elements, will continue to suggest opportunities to differentiate along multiple dimensions, including depth of clinical evidence, services, contracting, and branding. Biosimilar manufacturers will need to decide if pursuing interchangeability delivers a greater competitive advantage relative to alternative investments and initiatives.

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