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# Pricing and Market Effects of Biosimilar Entry in the US

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## 1. Introduction of Biosimilars in the US

The entry of biosimilars into the US pharmaceutical market is a very recent phenomenon beginning in 2015 with the launch of Zarxio.[1] Three biosimilars were added in 2016,[1] with five more predicted in 2017 at the time of this publication.[2] **Table 1** provides the name of each biosimilar date of FDA approval, name, and reference biologic name currently in the US market. **Table 2** provides biosimilars with goal dates on 351(k) applications under first-cycle review and reference biologic name.

**Table 1:** US Approved Biosimilars

| Date of FDA Approval | Biosimilar Name | Reference Biologic Name |
|---|---|---|
| March 6, 2015 | Zarxio | filgrastim/Neupogen |
| April 5, 2016 | Inflectra | infliximab/Remicade |
| August 30, 2016 | Erelzi | etanercept/Enbrel |
| September 23, 2016 | Amjevita | adalimumab/Humira |

Source: Greenberg P, Mortimer R, White A, et al. The biosimilar revolution is just beginning in the U.S. *Health Care Bulletin*, published online Fall 2016/Winter 2017, available at http://www.analysisgroup.com/biosimilar-revolution-just-beginning-us/ (accessed 4 April 2017).

**Table 2:** Biosimilars with Goal Dates on 351(k) Applications Under First-Cycle Review

| Goal Date | Proposed Biosimilar | Reference Biologic Name |
|---|---|---|
| January 2017 | Samsung Bioepis SB2 | infliximab/Remicade |
| June 2017 | Coherus CHS-1701 | pegfilgrastim/Neulasta |
| September 2017 | Mylan and Biocon MYL-1401O | trastuzumab/Herceptin |
| September 2017 | Amgen and Allergan ABP 215 | bevacizumab/Avastin |
| September 2017 (est.) | Beohringer Ingelheim BI 695501 | adalimumab/Humira |

Source: Sutter S. Biosimilars in 2017: crowded US FDA review queue, key legal decisions. *Pink Sheet, Pharma Intelligence*, published online 24 January 2017, available at https://pink.pharmamedtechbi.com/PS119882/Biosimilars-In-2017-Crowded-US-FDA-Review-Queue-Key-Legal-Decisions (accessed 4 April 2017).

Europe has experienced biosimilars since 2006, and thus can serve as an initial benchmark for insights through empirical studies that may be drawn for predicted effects for the US market.[3-5] The growth and interest in biosimilars will continue as the presence and spending on biologics increases. Biologics are predicted to account for a substantial share of global new active substances (NAS) available since 1996 in the year 2020 – specialty biologics (15%) and traditional biologics (12%), with orphan drugs (24%) being the largest segment where NAS are targeted.[6] Reimbursement systems in developed and pharmerging markets in response to growing cost pressures will seek to increase competition by encouraging utilization of lower-cost biosimilar alternatives.[7] Estimated global spending (and share of total sales) on biologics will have risen almost 5-fold from 2002-2017, $46Bn (11%) in 2002 to a predicted $221Bn (19-20%) in 2017.[7] Non-

original biologics (NOBs) products are also becoming more common in pharmerging markets given cost pressures and where patent protection of intellectual property is weaker.[7] Further, as evidence of cost pressure in developed markets, biologics now account for about 28% of all drug spending in the US yet comprise less than 1% of all prescriptions.[3]

The passage of the Biologics Price Competition and Innovation Act of 2009 in the US was recognition of the growing need to define a legal pathway for easier biosimilar entry to generate savings from the rising cost of biologics, take advantage of developments in the science to produce biosimilars, and leverage biosimilar experiences from Europe. Evidence that this act is succeeding are the growing number biosimilars under development and launched, with the following biologics having the greatest number of biosimilar candidates from pre-clinical/clinical to being marketed: adalimumab, rituximab, etanercept, bevacizumab, trastuzumab, pegfilgrastim, infliximab, and filgrastim.[8] However, questions persist regarding what defines interchangeability between a reference biologic and biosimilar, with guidelines needed from the FDA.[9] This issue has marketing implications for both biosimilars and reference biologics. Biosimilars will need to justify and compete why their drugs should be used by physicians and paid for by payers. This means acceptance of biosimilars with likely require further clinical studies to demonstrate equivalent clinical effectiveness to reference biologics. Reference biologics will find marketing and dissemination of further clinical and RWE evidence to be still useful to note areas of differentiation with biosimilar entry and mitigate substantial market share erosion.[8] This is one area of substantial difference between the biologic-biosimilar vs. branded-generic drug relationship. This means federal and state policies will greatly affect and determine biosimilar market penetration.[10] Furthermore, the cost savings potential for biosimilar drug use in the US is substantial. One cost saving estimate is about $44 billion over the period 2014 to 2024, measured as the reduction in direct spending on biologic drugs.[11] This estimate is highly dependent on FDA policies and regulations that affect the nature and extent of competition.[11] However, there are unique challenges facing biosimilar and even generic drugs in areas like cancer. Some researchers

conclude that biosimilar and generic anti-cancer drugs will not likely bend the cost curve in the US.[12] Nevertheless, even with unresolved legal issues regarding defining the meaning of interchangeability which will directly affect the level of market competition between biologics and biosimilars, there are ample opportunities for biosimilars to grow substantially further in the future. Thus, biopharma companies with reference biologics will want strategic and operational guidance on how to prepare for and respond to biosimilar entry, while understanding price and market effects.

This white paper will cover the following questions as they pertain to the entry of biosimilars in the US market:

- What are the barriers and determinants to biosimilar entry in a specific market? (section 2.1)
- What are the price impacts of biosimilar entry and resulting share changes of the reference biologic? (section 2.2)
- What is the pricing strategy effect on the reference biologic? (section 2.3)
- What effects do biosimilar entry have on messaging & marketing (role of promotion) for the reference biologic? (section 2.4)
- What differences should be expected for biosimilar adoption by payer and provider channels? (section 2.5)

## 2. Insights into Key Questions Involving Biosimilar Entry in the US

### *2.1 Barriers and Determinants to Entry*

Biosimilars face higher barriers to entry than small-molecule generic drugs. These higher barriers to entry will mean reference biologics will likely face less competition than traditional generic drug entry. This means less biosimilars within a specific market, less price competition and erosion, thereby implying limited share loss to the reference biologic, all things being equal. The following factors represent significant barriers to entry for biosimilars, as taken from the European experience:[5]

a. greater development costs and risks.

b. higher safety concerns.

c. greater complexities in manufacturing, distribution, storage (cold), required delivery devices, patient adverse reactions to a live organism.

d. pricing concerns in that the initial price point for the first biosimilar entrant may not be substantially below that of the reference biologic given an array of barriers, thus affecting affordability and patient adoption.

e. greater institutional market impediments such as a lack of physician and payer acceptance of the biosimilar as interchangeable to the reference biologic.

f. regulatory uncertainty regarding the degree of interchangeability established between the biosimilar and reference biologic.

g. attracting patients for clinical trials will be more challenging since these drugs service a small population (so finding patients will be more difficult), and the unwillingness of patients to be in a clinical trial and not receive therapy as part of the design that could benefit them (a biologic would already exist that could help them, so why risk not getting therapy).

h. the need for promotion by biosimilars to disseminate to healthcare system stakeholders, and especially physicians and payers, the nature of biosimilar-biologic interchangeability.

i. the expectation that large well-established companies are expected to dominate the market for biosimilars, thus have the resources to make it more difficult for multiple biosimilar entrants in the same market.

j. the need for pharmaceutical alliances given the higher risks inherent in biologic/biosimilar development.

k. possible extension of a patent for the reference biologic.

Similar comments about prevailing entry barriers facing biosimilars have been expressed elsewhere in the literature.[3,13]

The above barriers-to-entry factors will mean biosimilar manufacturers will target their development and launch efforts with the following characteristics:

l. chronic disease areas for which there is a long treatment timeline to allow for higher returns to recoup R&D costs.

m. existing reference biologics in areas of high unmet medical need, thus significant demand potential.

n. existing reference biologics with high price points for treatments, thus even with some reduction in the biosimilar price relative to the biologic, there is ample room for positive returns from R&D costs.

o. relatively lower R&D costs as compared to other potential reference biologics.

### *2.2 Price and Share Changes*

Market price and reference biologic share changes from the European experience affirm implications from the preceding barriers-to-entry factors. A detailed modeling and econometric analysis reveals the following general patterns and those to specific market situations (see Scott, Stern, Stern, 2017 for an excellent empirical analysis of the below-noted effects):

Price change effects (from European analysis)[3]

a. Prevailing market prices fall over time at a rate of about 3 percentage points per year following biosimilar entry. Steepest price declines were in the Epoetin and Filgrastim markets.

b. Small price declines for biosimilars where fewer biosimilar entrants exist, as in the case of Somatropin.

c. Greater price declines occurred in markets with higher biosimilar competition exist, as in the case of Filgrastim relative to Epoetin and Somatropin.

d. Greater number of non-procurement policies designed to encourage the use of biosimilars led to lower prices.

e. A review of US data, Zarxio (biosimilar to Neupogen) and Granix (quasi-biosimilar to Neupogen) shows the following price discount (share of sales) vs. originator six months after launch: Zarxio 15% (~10%), Granix ~11-23% (5-10%). These price and share effects are substantially different and lower than the generic drug average ≥40% (≥75%).[1]

Share penetration effects (from European analysis)[3]

f. Biosimilar share of total sales increases over time, approximately on average 6 percentage point increase in biosimilar penetration per passing year.

g. Significant variation in biosimilar penetration by year per case: 9 percentage points per year, Epoetin case; 4 percentage points per year, Filagrastim case; 2 percentage points per year, Somatropin case.

h. Stronger tenders are associated with higher rates of biosimilar penetration.

i. Greater number of non-procurement policies designed to encourage the use of biosimilars led to higher rates of adoption overall.

Substitutable vs. interchangeable effects on penetration (from European analysis)[3]

j. Strongest tenders (i.e., those with full demand) in countries most associated with biosimilars seen as interchangeable, only substitutable elsewhere.

k. Interchangeable biosimilars (i.e., strongest tenders) have about 15 percentage point higher penetration, like in the case of the Epoetin market, and where prices are 60% lower than the reference biologic price.

*2.3 Pricing Strategy Effect on the Reference Biologic* (predictions for the US market)

a. Unlike competition between traditional small-molecule brand-generic drugs, biologics-biosimilars will have differentiated competition on price and quality.[13]

b. How biologics-biosimilars are administered will affect pricing strategies. Many biologics-biosimilars are physician-administered drugs (PADs), thus included in Medicare Part B, not Part D. The nature of medical benefit insurance likely affects the direction of pricing strategy, and operates differently than formulary-based contracts where buyers are affected by movements in the price.[3]

c. Buying patterns of physicians to purchase and store biologics-biosimilars to ensure they have an available supply will also have an impact on the pricing approach.[3]

d. Biopharma companies will need to study buying patterns for physicians and hospitals in the use of biologics-biosimilars and create incentives for use.[3]

### *2.4 Effects on Messaging & Marketing for the Reference Biologic and Biosimilar* (predictions for the US market)

a. Unlike traditional small-molecule brand-generic drug competition where no role for marketing exists after generic entry, there is a more significant role for messaging & promotion for both biologics and biosimilars.

b. The role of messaging & promotion for biosimilars will be to disseminate quality and interchangeability (per regulatory guidelines), while for biologics, the role will be to note areas of differentiation.

c. Dissemination of clinical trial data and RWE for biosimilars will be critical to gain physician and payer acceptance.

d. Dissemination of clinical data and RWE for biologics will be critical to highlight areas of differentiation with biosimilars to physicians and payers.

e. The use of highly specialized and well-trained sales forces, MSLs (medical science liaisons), and technology to disseminate complex scientific information and sources of value will be critical to advance value propositions of either biologics or biosimilars to key healthcare stakeholders.

### *2.5 Differences in Biosimilar Adoption by Payer and Provider Channels* (predictions for the US market)

Payer channel[13]

a. Medicare and private plans - early indications suggest an evolving pattern. Pressures to contain costs will provide incentives to use biosimilar if supported by the clinical evidence.

b. Medicaid - pressures to contain costs and thus budget impacts at the state level will strongly encourage biosimilar use.

c. Hospital-based insurance - strongest economic incentives to use biosimilars.

Provider channel

d. Physicians – biosimilar use will depend on federal and state regulations governing interchangeability, demonstration of clinical evidence, and cost.

e. Hospitals - margin pressures on hospital operations will incent medical institutions to use biosimilars.

## 3. Conclusions and the Future of Biosimilars in the US Market

The entry of biosimilars into the US market provides opportunities for substantial savings.[11] The evidence from Europe suggests that previously held assumptions about small-molecule brand-generic drug competition and effects don't hold for the biologic-biosimilar dynamic. Significant entry barriers facing biosimilars will mean less competition for reference biologics resulting in lower price and share erosion effects relative to the originator drug. These predictions affirm previous biopharmaceutical company decisions to shift portfolios toward specialty medicines given the following factors:

- few remaining economically viable small-molecule targets to capitalize.
- increased genericization of markets and pressures from payers.

- seek out therapy areas with greater price flexibility and less competition.
- leveraging developments in the science to take advantage of biologic/biosimilar drug development.[14-15]

One consequence and trade-off for biopharma companies in moving toward specialty medicines is their cost, as evidence from the latest average R&D cost and risk estimates of $2.6 billion, with this figure higher for biologic medicines.[16] This means significant opportunities exist for biosimilars to undercut biologic prices while still reaping enough returns to pay for the higher complexities of producing and delivering biosimilars to the market.

The success and penetration of biosimilars to take away from reference biologic share will depend on the regulatory definition of interchangeability and demonstration of clinical trial evidence. Working in favor of biosimilars are substantial economic pressures on payers and patients to afford the latest specialty medicines (as evidenced in this white paper series, see Axtria Research Hub for papers, http://axtria.com/axtria-research-hub-pharmaceutical-industry/). While the early period of biosimilar entry in Europe reveals limited penetration, as biosimilars have become more prominent and accepted by physicians, their adoption has grown. Such is the pattern expected for the US market, provided the regulatory/legal environment allows for biosimilar penetration. Biopharmaceutical companies with reference biologics facing potential biosimilar competition will need to develop critical expertise across an array of areas to differentiate successfully biologic vs. biosimilar benefits and costs. These areas include combining HEOR and RWE biostatistics modeling with traditional commercial analytics, rethinking the existing commercial model design (CMD) and internal organizational structure, developing new data capabilities from patient claims and electronic medical records to support these new model designs, and using technology to take strategic policies to successful execution.[17]

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