

Lessons for the United States from Europe's Biosimilar Experience

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EXECUTIVE SUMMARY

As the United States marks the tenth anniversary of the establishment of a biosimilars pathway, many experts express frustration that the US lags behind Europe. This paper carefully examines the US and European biosimilars markets and finds that the comparison between the markets is nuanced. In fact, after adjusting for differences in the approval pathways and markets, the United States is currently in parity with Europe in terms of the number of reference biologics with an approved biosimilar. And Europe is generally, but not always,

ahead of the United States in terms of market maturity, number of biosimilar competitors for each reference biologic, and biosimilar market share.

While Europe is often touted as the ideal market for biosimilars to flourish, the experience in reality differs from country to country. This paper delves into the lessons the United States should adopt to speed the development of its market while also highlighting European market pitfalls to avoid.



CAUTIONARY LESSONS



LET COMPETITION DRIVE PRICES

Policymakers must allow robust competition to bring prices down rather than using European-style price controls, which risk discouraging biosimilar manufacturers from entering or remaining in the market



SET REASONABLE MARKET EXPECTATIONS

Market participants should not anticipate eye-popping biosimilar price discounts like those won through European reimbursement and pricing systems that could threaten sustainable competition and supply



LESSONS TO FOLLOW



PROMOTE BIOSIMILAR EDUCATION

Stakeholders — including regulators, providers, manufacturers, patient advocates, physicians, and health plans — should engage in extensive and collaborative education campaigns to promote awareness and acceptance of biosimilars



INCENTIVIZE UPTAKE

Decision-makers across the healthcare system, including government programs, should push biosimilar uptake by setting utilization targets and creating incentives for uptake by sharing biosimilar savings with providers and patients



SHARE CLINICAL DATA

With the science of biosimilars settled and their track record for safety and efficacy on strong footing, the FDA should continue to explore a global comparator or reference program to increase the efficiency of biosimilar development and approval, as the agency highlighted in its 2018 Biosimilars Action Plan



ALLOW THE PATHWAY TO EVOLVE

As biosimilar manufacturers and regulators gain experience and confidence, and technology advances, regulators should maintain flexibility — grounded in science — in requirements for and review of biosimilar applications

The development of the US biosimilars market often is cast in the shadow of Europe’s earlier entry into the arena. A decade after the United States established its own biosimilars pathway, it is time to move beyond this outdated perception and consider what the United States can learn from Europe’s longer — but not necessarily more successful — experience with biosimilars. In this paper, we address several misconceptions often present in a comparison of the US and European markets and identify both cautionary lessons for the US biosimilars industry and lessons the United States would do well to follow.

ANALYSIS OF US AND EUROPEAN BIOSIMILARS MARKETS

Parity in Approvals

Fifteen years ago, the European Union (EU) led the world in establishing a regulatory pathway for biosimilars to enter the market and compete with reference biologics. In 2006, the European Medicines Agency (EMA) approved the first EU biosimilar, Omnitrope (somatotropin). In the EU today, 58 biosimilars are approved for 16 reference products (*GaBI, 2020a*) (see Figure 1).

In the United States, the Biologics Price Competition and Innovation Act (BPCIA), part of the Affordable Care Act of 2010, created a US biosimilars pathway. In 2015, the US Food and Drug Administration (FDA) approved the first US biosimilar, Zarxio, whose reference biologic is Neupogen (filgrastim). The FDA approved three more biosimilars in 2016, five in 2017, seven in 2018, and ten in 2019, for a total of 26 approvals, corresponding to nine reference products (*FDA, 2020*) (see Figure 1).

The Opportunity for Biosimilars in the United States

Because biologics are made from living cells and not chemical compounds, they are not eligible for the US regulatory pathway established more than 35 years ago to facilitate the approval of generic copies of small-molecule drugs.

A US biosimilars pathway was created in 2010, and biosimilars have already begun to bring savings to the healthcare system and improve patient access. The FDA has approved 26 biosimilars in total

with 30 more under review, and competing biosimilars are available for seven biologics.

But more biosimilars and more robust competition are needed. Reference biologics today still represent three of the top five drugs and seven of the top 20 drugs by sales in the United States (*Statista, 2020*). Nearly \$124 billion — more than a third of all US prescription drug spending — was attributable to biologics in 2018 (*IQVIA, 2019a*).



Biologics represent 36% of US drug spending

Source: IQVIA, 2019a.

FIGURE 1. APPROVED BIOSIMILARS: UNITED STATES VS. EU

ACTIVE SUBSTANCE	BIOSIMILAR APPROVED IN EU?	BIOSIMILAR APPROVED IN US?
Adalimumab	✓	✓
Bevacizumab	✓	✓
Epoetin alfa	✓	✓
Etanercept	✓	✓
Filgrastim	✓	✓
Infliximab	✓	✓
Pegfilgrastim	✓	✓
Rituximab	✓	✓
Trastuzumab	✓	✓
Epoetin zeta	✓	No US reference product
Enoxaparin sodium	✓	Approved as NDAs, not BLAs*
Teriparatide	✓	
Follitropin alfa	✓	Deemed BLAs on March 23, 2020*
Insulin glargine	✓	
Insulin lispro	✓	
Somatropin	✓	

* US reference biologics are approved by the FDA through Biologics License Applications (BLAs). Six of the active substances with biosimilars approved in the EU but not in the United States were previously approved by the FDA through New Drug Applications (NDAs) for small-molecule drugs. Four of these six products were just deemed to be BLAs on March 23, 2020 (FDA, 2019a), while two will remain NDAs.

It is important to note that, as **Figure 1** demonstrates, the biosimilars approved in the EU that are not approved in the United States are ineligible or have only just become eligible for the US biosimilars pathway. In other words, the United States is currently in parity with the EU in terms of the number of reference biologics with an approved biosimilar after adjusting for differences in the approval pathways and markets.

Of the 26 biosimilars approved by the FDA, 17 are on the market, corresponding to 7 reference products (see **Table 1**).¹ By the end of 2019, 17 percent of US biologics sales faced biosimilar competition (*IQVIA, 2020*), compared to 21 percent in Europe (*IQVIA, 2019b*).

¹ The two reference biologics with first-time biosimilars approved but not launched are Humira (adalimumab) and Enbrel (etanercept). Five adalimumab biosimilars and two etanercept biosimilars have been approved, but patent challenges against Enbrel have been unsuccessful, and the numerous Humira patents asserted by AbbVie against biosimilar manufacturers, as well as the uncertainty surrounding the patent situation, drove biosimilar manufacturers to settle.

TABLE 1. 17 US BIOSIMILARS MARKETED FOR 7 REFERENCE PRODUCTS

REFERENCE PRODUCT	ACTIVE SUBSTANCE	# OF BIOSIMILARS LAUNCHED
Avastin	Bevacizumab	2
Epogen/Procrit	Epoetin alfa	1
Herceptin	Trastuzumab	5
Neulasta	Pegfilgrastim	3
Neupogen	Filgrastim	2
Remicade	Infliximab	2*
Rituxan	Rituximab	2

* 2 additional approvals

Distinctions Between Markets

There are three ways that Europe is measurably ahead of the United States in its biosimilars market, though not without some qualification.

1) Maturity of the market. As mentioned above, the first biosimilar was approved in Europe nearly a decade before the first US biosimilar was approved in 2015. And the US biosimilars market is still nascent. In fact, 11 of the 17 biosimilars marketed in the United States have launched since January 2019. And three of the seven reference biologics with US biosimilar competitors (Avastin, Herceptin, and Rituxan) only began facing competition in the last 11 months. That said, the European biosimilars market as it exists today is relatively new, with more than half of all current biosimilars approved since 2017 (*GaBI, 2020a*).

2) Number of competitors. Almost across the board, the EU has approved more biosimilars for each reference biologic than the United States. For example, Neupogen (filgrastim) and Neulasta (pegfilgrastim) each have seven biosimilars approved in the EU, compared to two and three approved (and marketed), respectively, in the United States. Only Herceptin (trastuzumab) has as many biosimilars approved in the United States (five) as are approved in the EU. However,

EMA-approved biosimilars are not necessarily available in every EU country, and the FDA has more than 30 biosimilar applications in review (*FDA, 2019b*) compared to 14 in review at the EMA (*GaBI, 2020b*).

3) Biosimilar market share. The most successful US biosimilar thus far (the first, Zarxio) has achieved nearly 55 percent of the US filgrastim market (*Hagen, 2020*). But biosimilars' experience has been characterized by slow uptake in the United States. A new analysis of the largest US commercial health plans' coverage decisions related to biosimilars found that only 14 percent of decisions gave preferred coverage to the biosimilar (*Chambers et al., 2020*). While Europe is frequently credited with far higher biosimilar uptake – even 100 percent in some cases – Europe's dominance in this area is often overstated. While some European countries have very high biosimilar market share in certain therapeutic areas, biosimilar uptake differs from country to country in Europe and can vary significantly by product class (*IQVIA, 2019b*). For example, 16 European countries achieved greater than 90 percent biosimilar utilization for filgrastim and pegfilgrastim in 2018, but utilization in Ireland was just 27 percent (*IQVIA, 2019b*). And among anti-tumor necrosis factor biosimilars (adalimumab, etanercept, and infliximab), Norway and Denmark had 81 percent and 96 percent biosimilar uptake, respectively, but every other country's utilization was below 50 percent (*IQVIA, 2019b*). In addition, as we discuss below, some practices in European countries that allow biosimilars to achieve a high market share would not create long-term, sustainable competition among biologics and biosimilars in the United States.

In short, the European biosimilars market as a whole is not markedly different from the US market after accounting for its longer existence. That said, there are certainly lessons the United States can draw from Europe's experience – both cautionary lessons and ones we should follow.



CAUTIONARY LESSONS

The cautionary lessons from Europe relate to 1) the importance of competition in the biosimilars market and 2) reasonable expectations for the market, including prices. Biosimilars involve substantial risk, time, and expense to develop. Some practices in Europe, if adopted in the United States, would prove detrimental to the long-term sustainability of the US biosimilars market.

Price Controls vs. Competition

The development of biosimilar pathways in the United States, Europe, and elsewhere afford health systems the opportunity to realize cost savings associated with a more competitive biologic drug marketplace instead of the higher pricing associated with a monopolist manufacturer. The best way to arrive at these savings is by having multiple competitors on the market, which drives prices toward the marginal cost of manufacturing these drugs, making them more affordable. However, some policymakers in Europe believe that biosimilar prices should be set artificially. For example, in Poland, the first biosimilar must be 25 percent cheaper than its reference biologic, and the second biosimilar must be further discounted; in the Czech Republic, Finland, Latvia, and Serbia, the first biosimilar must be priced 30 percent lower than the reference biologic (*Moorkens et al., 2017*).

Mandatory discounts and related strategies are short-sighted because they could thwart a sustainable biosimilars market. Over time, price controls, especially when set by regulators driven to maximize short-term savings, can force prices too low. This can discourage biosimilar entrants and lead existing producers to exit the market. In the United States,

the risk of price controls could discourage drug manufacturers from embarking on the costly and time-consuming process of developing and seeking approval for a biosimilar.

Maximizing cost savings from biosimilars can be realized in a sustainable way by facilitating approvals and a robust competitive marketplace, not by setting prices so that manufacturers are discouraged from entering the market entirely.

Market and Pricing Expectations

Many European health systems have adopted a process known as tendering to award a contract for the supply of a particular biologic (reference product or biosimilar) to the manufacturer with the lowest bid and proven capacity to supply. Twelve European countries have single-winner tenders (*Simoens and Cheung, 2020*). The opportunity for a manufacturer to win such a large contract can induce a “race to the bottom” on prices and instability in production. While the tender might result in a very low price for the duration of the contract, in the long term, the price may deter new entrants.

In addition to concerns about supply and impact on the long-term competitiveness of biosimilar markets, tendering also creates inaccurate expectations for biosimilar prices. The degree of competition and price discounts that can be expected for biosimilars is distinct from the traditional small-molecule drug market, where generic substitution and discounts are typically very high because barriers to entry and production costs are low. Biosimilar manufacturers face relatively steep barriers to entry and higher development and manufacturing costs. For example, estimates of the development cost for a new biosimilar range from \$100 million to \$300 million per biosimilar, many multiples higher than the fixed costs associated with a new small-molecule generic

drug. Market-based competition among reference biologics and biosimilars – in contrast to tendering – will result in lower average prices and will also ensure an adequate risk-adjusted return on the investment required to bring new biosimilars to market.

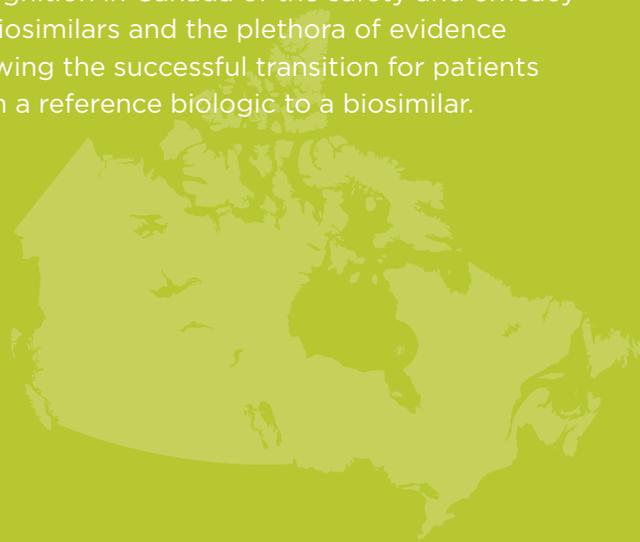
Recently, some European countries have developed more nuanced tendering processes – for example, by awarding multiple contracts to mitigate the risk of having a single supplier. While better than a single-winner tender, these arrangements still risk creating volatility in capacity utilization for biosimilar manufacturers.

Biosimilars in Canada

Our neighbor to the north has recently seen provinces move to encourage biosimilar utilization, beginning with British Columbia in 2019. In two phases, first for patients with rheumatoid arthritis followed by gastroenterology patients, British Columbia successfully moved more than 22,000 patients to biosimilars.

A program to move patients to biosimilars is currently in progress in Alberta, and Ontario plans to follow suit. The provinces plan to put the millions of dollars in savings from biosimilar utilization back into their health systems.

These developments highlight the growing recognition in Canada of the safety and efficacy of biosimilars and the plethora of evidence showing the successful transition for patients from a reference biologic to a biosimilar.





POSITIVE LESSONS

Despite these cautionary lessons, there are aspects of the European biosimilars experience that provide positive guidance for the United States. Below, we highlight four of these areas. US stakeholders are generally moving in these directions already, but they should make a concerted effort to advance more rapidly.

Education Campaigns

One area in which many European countries have excelled is how quickly and widely policymakers and others have grasped the significance of physician and patient awareness and acceptance of biosimilars. The EMA, individual European countries, and other stakeholders have launched successful education campaigns designed to foster comfort with and confidence in the safety and efficacy of biosimilars.

EXAMPLES FROM EUROPE...

Germany has been touted for its “significant investment in physician education” (*EY, 2017*).

- “Physicians [in Germany] were approached by their Kassenärztliche Vereinigung (KV, regional physicians’ association) early on, using open communication channels and discussion forums to build trust in the biosimilar concept” (*IMS, 2016*).

The European Specialist Nurses Organisation (ESNO) drew praise for issuing a guide specifically

for nurses who handle switching patients between biologics and biosimilars.

- “Switch Management Between Similar Biological Medicines: A Communication and Information Guide for Nurses,” originally only available in English, was recently released in seven additional languages: Dutch, French, German, Italian, Polish, Portuguese, and Spanish. ESNO plans to continue translating the guide into other EU languages (*Center for Biosimilars, 2019*).

IN THE UNITED STATES...

Recently, the FDA began producing educational materials aimed at healthcare providers and patients. Other stakeholders, from manufacturers to patient advocacy organizations, are supplementing this effort. It will be important for more stakeholders, including physicians associations and health plans, to engage in education campaigns and begin to think more comprehensively about raising awareness and acceptance. Achieving widespread familiarity

and comfort with biosimilars will require not just a one-directional flow of information, whether from regulators to physicians and patients or from physicians to their patients, but also lateral communication, including healthcare provider to healthcare provider and patient to patient. Ultimately, the confidence in biosimilars among all actors in the healthcare market must reach the level of acceptance of generic drugs.

Targets and Incentives for Biosimilar Uptake

Some European countries and regions have had success with setting specific targets for biosimilar uptake. For example, France and the United Kingdom (UK) have each set 80 percent biosimilar utilization targets. While some countries have required the use of biosimilars, other strategies for meeting targets have been helpful in encouraging biosimilar uptake. These include incentives for providers to prescribe biosimilars as well as sharing benefits with patients, known in Europe as gain-sharing.

EXAMPLES FROM EUROPE...

Germany and the UK are among more than a dozen countries across Europe that offer provider incentives to prescribe biosimilars (*Moorkens et al., 2017*).

- In Germany, “gain-sharing arrangements are established at the payer level. For example, physician association KV Westfalen-Lippe and the SHI Barmer GEK have a contract where any cost saving realized by primarily prescribing infliximab biosimilar for patients with ulcerative colitis or Crohn’s disease will be equally split between the treating physician and Barmer GEK” (*Pant et al., 2018*).
- In the UK, NHS England offers providers 1 percent of the contract value of biosimilars if they start 90 percent of new patients on a biosimilar and switch 80 percent of existing patients (*Pant et al., 2018*).

France and the UK have created programs to share the benefits of biosimilar savings with patients.

- “Transparent reallocation of the biological medicines budget has been introduced in the United Kingdom and more recently in France, by means of a pilot project whereby the prescription of a selection of biosimilar medicines rewards the hospital departments involved in the prescription for reinvestment in patient care” (*Maréchal-Jamil, 2019*).

IN THE UNITED STATES...

Pharmacy benefit manager (PBM) Magellan Rx Management reported in 2019 that its dedicated efforts to promote infliximab (a biosimilar for Remicade) had helped its health plans achieve 75–86 percent utilization of infliximab (*Magellan, 2019*). In January 2020, the nonprofit plan Health New England reported that Magellan Rx’s initiative had resulted in 93 percent infliximab uptake (*Taylor, 2020*). Decision-makers across the US

healthcare system, including government programs, should push this kind of biosimilar initiative. They should also consider sharing biosimilar savings in some fashion with providers and patients (see *Brill, 2020*). Shared savings programs have become common in Medicare and could be extended to biosimilars, while private health plans could set up their own shared savings programs.

Confidence in Clinical Evidence and Switching

In Europe's nearly 15 years of experience with biosimilars, a plethora of clinical evidence has been amassed showing that biosimilars are safe and effective. In addition, "no interruption in therapeutic outcomes have been seen to date" in the switching of European patients from a reference biologic to a biosimilar (*Wolff-Holz et al., 2019*). A new comprehensive review of 178 switching studies in the EU found that "available switching data do not indicate that switching from a [reference biological product] to a biosimilar is associated with major efficacy, safety or immunogenicity issues" (*Barbier et al., 2020*).

EXAMPLES FROM EUROPE...

In Norway and Denmark, where biosimilar uptake exceeds 80 percent, "no unexpected issues have been discovered after more than a decade" (*Katsoulis et al., 2019*).

In Germany, a new law is in the process of being implemented to allow for biosimilar substitution at the pharmacy level – an indication of confidence in biosimilars.

In Italy, the national medicines agency, AIFA, recently published an analysis examining the safety of biosimilars in order "to help citizens and healthcare professionals in the use of these medicines, improving their understanding of therapeutic efficacy and the possibility of switching between biological therapies" (*Wallace, 2019*).

IN THE UNITED STATES...

Every FDA-approved biosimilar has been shown to have no clinically meaningful difference from its reference product, but data on real-world utilization can help with public perception and confidence. With a decade's head start on the United States, Europe has a longer track record with biosimilars' safety and efficacy, but evidence is certainly not unique to Europe. In the United States, the integrated healthcare system Kaiser Permanente recently published a study detailing the successful switch of adult patients with inflammatory bowel disease from the reference biologic Remicade to a biosimilar infliximab (*Ho et al., 2020*). Incidentally, Kaiser has achieved greater than 80 percent biosimilar utilization for infliximab, as well as four other biosimilars – bevacizumab, filgrastim, rituximab, and trastuzumab – in some cases within weeks (*Welch, 2020*).

The United States should also engage in data sharing with Europe. The FDA, in its Biosimilars Action Plan, has acknowledged this potential, stating, "We are also exploring data sharing agreements that can give us better insights into biosimilars' real world safety and efficacy and, in some circumstances, facilitate the increased use of non-U.S.-licensed comparator products in certain studies to support an application under section 351(k)" (*FDA, 2018*).

Unfortunately, there have been insidious attempts in the United States to undermine the clinical evidence on biosimilars from Europe. In fact, "There are ongoing efforts to suggest significant weaknesses in European safety reporting" (*Cohen and McCabe, 2019*). The FDA has recently teamed up with the Federal Trade Commission to fight misinformation about biosimilars. This should include the misrepresentation of data from Europe.

Regulators' Willingness to Evolve

In Europe, there has been evidence of regulators being open to the evolution of the biosimilars pathway and a willingness to work with industry as the biosimilars market matures to streamline the application and approval processes.

EXAMPLES FROM EUROPE...

Revised guidelines. Biopharmaceutical researchers have emphasized the importance of regulatory evolution in the EU:

Revised versions of the EMA's overarching biosimilars guideline and nonclinical and clinical issues, for example, came into effect in 2015. The updated guidance allows clinical trials conducted using reference medicines authorized outside the European Economic Area to be used for the EU filing. In the past, these trials would have had to be repeated in European patients, using an EU-approved reference medicine, at extra cost to the sponsor. (*Schiestl, Zabransky, and Sörgel, 2017*)

Flexibility for development programs. A recent study of European public assessment reports on biosimilars found that regulators showed flexibility in approving applications with innovations in study designs, patient population choice, and other areas:

Regulators in Europe seem to be open to discuss alternative development strategies. This was observed in cases in which a biosimilar has already been approved and used, and also in cases in which a product-specific guideline exists. Therefore, sponsors who would like to structure the development programme in a different way might have a fair chance of gaining approval in the end, if the alternative approach can be justified from a scientific point of view. (*Mielke et al., 2018*)

IN THE UNITED STATES...

The FDA appears to recognize the need to evolve standards over time. For example, the director of the agency's Office of Therapeutic Biologics and Biosimilars, Sarah Yim, recently acknowledged, "I think everybody knows that we have to move away from always thinking about two clinical trials for everything, for new drug development as well as clinical studies for every biosimilar development program" (*Cipriano, 2020*). A new review of EU and US biosimilar approvals found that there is "no routine need for comparative efficacy trials" (*Schiestl et al., 2020*).

As biosimilar manufacturers and regulators gain experience and confidence, and technology advances, this kind of flexibility – grounded in science – will be important for fostering a thriving US biosimilars market. A maximally streamlined development, application, and approval process will be all the more vital for biosimilars of orphan or small-market biologics. Because manufacturers will have greater difficulty recouping costs for developing biosimilars of small-market biologics, they may not enter these markets at all if the costs are deemed too high (see *Brill, 2015*).

Conclusion

The comparison between the European and US biosimilars markets is more nuanced than many recognize, and there are important ways that the US market should depart from Europe's experience in order to better foster competition. But European policymakers and regulators have pursued some strategies that would help encourage biosimilar uptake in the United States. US stakeholders have, to some extent, begun to pursue these strategies independently, but if we want to see the US biosimilars market take off in its second decade of existence, they should be embraced fully.

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