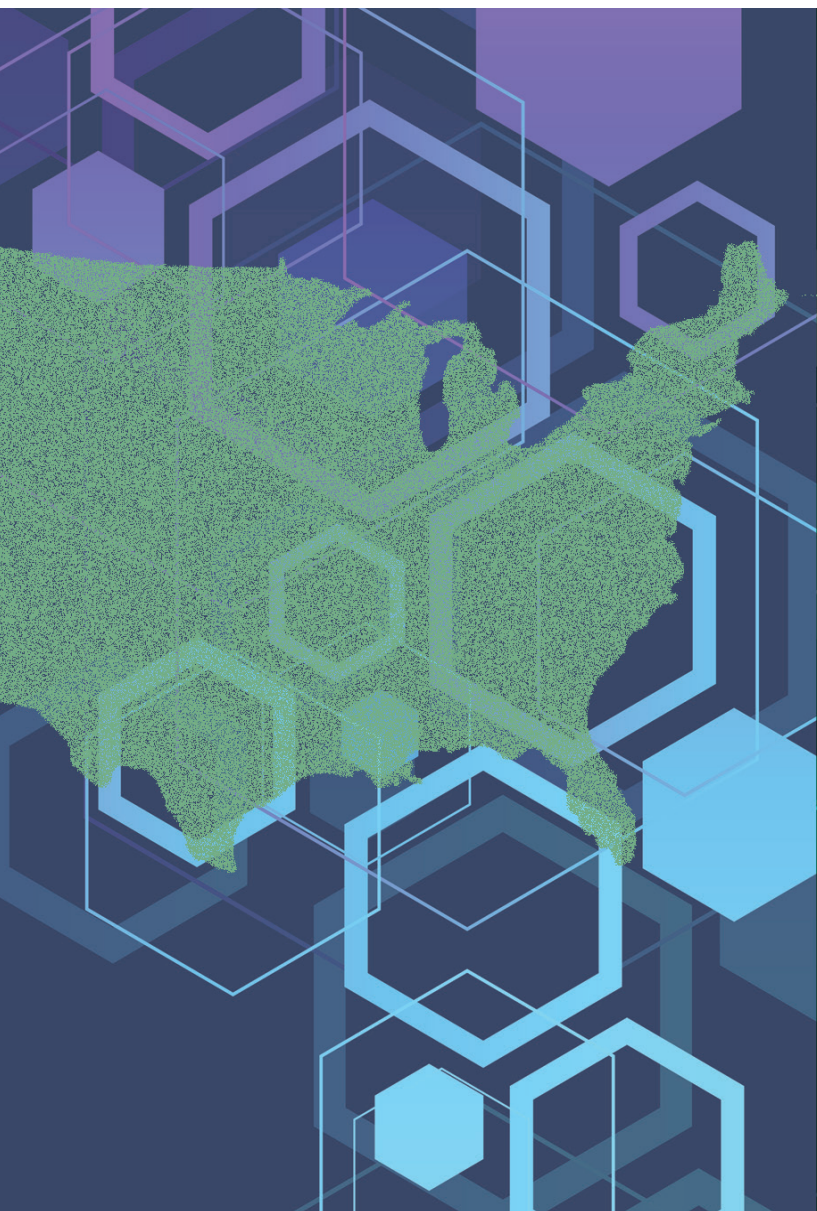


# REALIZING THE BENEFITS OF BIOSIMILARS:

What the U.S. Can Learn from Europe

*A Guide for U.S. Policymakers*



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## Abstract

The United States enacted a pathway for the approval of biosimilar medical products in 2010, but uptake and use of these products have lagged greatly in comparison to Europe. As a result, it is likely that the U.S. has forgone considerable savings that could have accrued from competition from lower-priced biosimilars as compared to those of the original reference products. This paper explores the differences in the market conditions for biosimilars in the U.S. compared to various European countries that have contributed to the gap in biosimilar uptake and use. It also offers key lessons from the European experience that could inspire changes in U.S. regulatory and payment policy and encourage far greater use of biosimilars. Among the most important are streamlining the regulatory approval process for biosimilars at the U.S. Food and Drug Administration; taking steps to deter developers of the original reference products from product creep and obtaining multiple patents on incremental changes to the reference product that delay or block biosimilars competitors; revising Medicare payment systems to incentivize biosimilars use; and undertaking communication with patients, providers, and others to raise awareness and trust of biosimilars and fight misinformation.

## Introduction

Biologic drugs, or biologics, are products derived from living organisms or their components that treat a number of conditions such as diabetes, cancer, and immune disorders. Biologics range from relatively small molecule insulins, to monoclonal antibodies (mAbs), to cell and gene therapies and include some of the most expensive and profitable drugs on the market. As a result, there has been a longstanding push to create “biosimilars” that can compete with original biologic products, after a period of exclusivity, to balance incentives to innovate with less costly access to these important biologic therapies.

The United States (U.S.) adopted legislation to create a process for regulating and approving biosimilars in 2010. The law raised expectations that billions of dollars would be saved annually as multiple competitor biologics came onto the market at prices below those of the original drugs. More than a decade later, the promise of biosimilars in the U.S. has not fully lived up to these expectations. The reasons are complex and span a number of areas related to barriers to entry; uncertainties in the U.S. regulatory process; legal issues involving intellectual property; the ways in which biosimilars are covered and reimbursed by Medicare and private insurers; and clinicians’ and patients’ knowledge and acceptance of biosimilars, among other factors.

Meanwhile, other countries, most notably in Europe, have moved more quickly to adopt biosimilars, and now have more biosimilars on the market and in broad use. Those countries have differing regimes governing drug regulation, intellectual property, and pricing and payment. Many of these policies are not readily transferable from one to another; nonetheless, there are key lessons from their experiences that have relevance for the U.S.

This paper seeks to highlight these lessons learned by providing background on the availability and use of biosimilars in the U.S. and European environments, exploring what might be learned from applying the European experience to the U.S. setting, and providing potential steps to increase the pace of biosimilars approvals and expand their use in the U.S.

## Background

Biologic drugs are large molecules derived from living organisms and further engineered in laboratories. They are usually much more complex than “small molecule” drugs that are relatively simple chemical compounds manufactured by chemical synthesis. Many biologics were developed to treat conditions that previously proved difficult to treat effectively, including cancers, autoimmune, and inflammatory conditions such as rheumatoid arthritis and Crohn’s disease. Consequently, biologics are substantially more difficult and expensive to develop and manufacture than small molecule drugs, with complex manufacturing processes that result in batch-to-batch variability of the same originator biologic.<sup>1</sup>

Given their growing availability and high prices, biologics make up an increasing share of the nation’s overall spending on pharmaceutical drugs. Although they constitute only about 2% of all prescriptions in the U.S., biologics account for 43% of total drug expenditures,<sup>2</sup> and have accounted for over 90% of the growth in net drug spending in the country since 2014.<sup>3</sup> Some of Medicare Part D’s highest-expenditure drugs and all 10 of the highest-expenditure drugs in Medicare’s Part B program (where biologics are typically covered) are biologics,<sup>4</sup> thus accounting for a great share of Medicare’s drug spending.<sup>5</sup> Many commercial insurers face a similar situation, reporting that the largest share of their outlays for biopharmaceuticals are for biologics.

In the 1980s, the Drug Price Competition and Patent Term Restoration Act (also known as the Hatch-Waxman Act) established a pathway for the approval of generic versions of small-molecule drugs if the sponsor could establish “bioequivalence” with the original drug. Demonstrating bioequivalence is straightforward for most drugs: because the molecule is identical, equivalence requires that the generic is absorbed and metabolized by the body at a similar rate and extent as the original.<sup>6</sup> Since the passage of the Hatch-Waxman Act, generic drugs have generally become a success story in the U.S.—their utilization is very high, around 84% of all prescriptions, and prices decline sharply as more competitions enter the market. In fact, the U.S. both pays less for generics and uses more of them compared to other OECD countries.<sup>7</sup>

In the 2000s, multiple countries including the U.S. proposed and implemented regulatory pathways for approving biosimilar products that could be marketed once the original biologics lose their patent protection. The greater complexity of biologics manufacturing plus the potential for differences in bioequivalence across highly similar but not identical products mean that achieving cost reductions through competition in the large molecule space is more challenging. Nonetheless, with increasing use and spending on biologics, the opportunities for saving without compromising effectiveness of therapies are substantial and growing.

For reasons described below, European officials acted swiftly in comparison to their U.S. counterparts to establish a new regulatory regime for biosimilars. The European Medicines Agency (EMA), the European Union’s equivalent of the U.S. Food and Drug Administration (FDA), developed a biosimilars approval pathway in 2003 and approved the first biosimilars products for use in the EU in 2006. It took the U.S. an additional four years to adopt the Biologics Price Competition and Innovation Act (BPCIA) to create an

alternative approval pathway under the FDA for biosimilars. The first U.S. biosimilar was approved in 2015 for the molecule filgrastim. However, biosimilars for filgrastim had been approved in Europe as early as 2008.

The almost decade-long head start on biosimilars approvals is a major factor to broader use of biosimilars in Europe versus the U.S. Although the market penetration of biosimilars varies by country, the European biosimilar market is the largest in the world in terms of share of total global sales.<sup>8</sup> As of publication of this brief, Europe has approved 67 biosimilars, all of which entered the market (nine have since been withdrawn for commercial reasons). While experience has varied across countries and molecules, biosimilars attained the majority of the market share<sup>9</sup> and resulted in savings between 75-90 percent off the reference product prices.<sup>10</sup>

In contrast, the U.S. has 33 FDA-approved biosimilars,<sup>11</sup> of which just 18 have been launched thus far. The biosimilars that have launched in the U.S. are estimated to have only about 20% of the volume share of the biologic market that is accessible to biosimilars,<sup>12</sup> with savings in the 30-40 percent range off reference prices.<sup>13</sup> With additional biologic products losing their exclusivity over the next several years, addressing barriers to biosimilars entry is critical for realizing their savings potential.

The pace of biosimilar approvals and drug launches in the U.S. is increasing, and the market share of biosimilars is rising. However, the European experience illustrates how factors besides time can bring more biosimilars to market and facilitate their achieving higher market penetration rates. In this paper we review the regulatory, intellectual property, pricing and payment, and education and awareness issues behind biosimilars adoption and use; the ways in which other countries, particularly in Europe, have approached these issues differently from the U.S.; and the implications for potential U.S. policy reforms.

## Regulatory Issues

The U.S. and European regulatory environments for follow-on biologic products are aligned in some key respects. Both require demonstration that the biosimilar is highly similar to the original reference product—realizing that not even all versions of the *original* product are the same. Both the FDA and European regulatory agencies require that there be *no clinically meaningful differences* between the biosimilar and the reference medicine in terms of safety, efficacy, and quality. Originator and biosimilar manufacturers must also meet the same stringent requirements for good manufacturing processes. As the FDA notes, “slight differences are expected during the manufacturing process for biological products, regardless of whether the product is a biosimilar or a reference product.”<sup>14</sup>

Because of their greater complexity, more extensive clinical studies are generally needed for biosimilars than for small-molecule drugs to demonstrate the absence of clinically meaningful differences. A key issue for biosimilar entry and competition is thus the regulatory requirements for biosimilar developers to demonstrate sufficient similarity or equivalence of their products to the original reference products. Most important for the time and cost of biosimilar development is the extent to which scientific evidence enables regulators to conclude that the biosimilar has no clinically meaningful difference without requiring large, costly clinical trials of comparative safety and effectiveness to the originator product.



Within this framework, the U.S. and European regulatory environments differ in three key ways: the track record of the approval process flexibility, the existence of the so-called interchangeability designation, and the nonproprietary naming of biosimilars. The following section highlights these differences and implications.

#### *Flexibility of the biosimilar approval pathway*

The EMA has taken steps to identify more expeditious pathways for biosimilar approval. It has done so by building on advances in characterization techniques—the analytical approaches to understanding how complex molecules works in the body—as well as through increased understanding of pharmacology and disease processes.<sup>15</sup> Based on this scientific foundation, EMA has waived strict requirements for both comparative clinical efficacy studies for certain product categories, and comparative studies on safety and immunogenicity—the ability of a substance, such as an antibody, to provoke an immune response—in specific circumstances.<sup>16</sup> When EMA has already issued a product-specific guideline, the agency has been amenable to alternative clinical development strategies in areas such as innovative study designs or choice of patient populations if the product sponsor has a strong scientific rationale for a specific development program.<sup>17</sup>

Over the past decade and a half of biosimilar experience, these streamlined approval pathways have not been associated with discernible differences between the original reference product and biosimilar on patient outcomes, safety, immunogenicity, or efficacy. In addition, no difference has been shown in the nature, severity, or frequency of adverse effects from using biosimilars versus the original reference products.<sup>18</sup>

With such post-marketing safety experience and monitoring, and continued development of translational science, many regulatory experts argue that the EMA can further expand the role of analytical testing and pharmacokinetic (PK) studies,<sup>19</sup> eliminating the need for costly comparative efficacy trials in a growing range of circumstances.

Like the EMA, the FDA has the authority to waive the requirement of a comparative clinical study if it is deemed unnecessary to support approval based upon totality of the evidence, and has waived these studies for several biosimilars.<sup>20</sup> FDA officials have acknowledged that the agency needs to move away from always requiring a clinical trial for every biosimilar development program.<sup>21</sup> In addition, the U.S. approval pathway could potentially be accelerated with more use of real-world evidence (RWE) from Europe regarding the safety and efficacy of biosimilars, which as noted above, have not detected differences in the nature, severity, or frequency of unexpected adverse events versus the originator reference products.

#### *Moving from biosimilarity to interchangeability*

Another difference between the European and U.S. regulatory regimes pertains to the FDA's ability to designate some biosimilars as "interchangeable" with their reference products. Unlike small molecule generics that are "AB rated" and can be automatically substituted for their reference drugs at the pharmacy counter, biosimilars cannot be substituted for their reference products without a prescriber's intervention unless they obtain an additional regulatory designation of "interchangeability." Many states have passed their own laws that further restrict in what circumstances substitution of biosimilars

can apply, typically imposing additional requirements that do not apply to generics, such as post-substitution notification.<sup>22</sup>

To achieve interchangeability, the FDA requires a manufacturer to provide data and information to evaluate the risk, in terms of safety and decreased efficacy, of alternating or switching between the products, if the product is administered to a patient more than once. These precautions were based on a concern with immunogenicity – the ability of a molecule or substance to provoke an immune response – from switching, a concern that has not materialized<sup>23</sup> with any European or U.S. market experiences with switching. In addition, this designation does not enable switching between different biosimilars to the same reference product.

By contrast, the EMA does not have an *interchangeability* designation as a legal or regulatory matter. EU member states do not require additional clinical studies, such as switching studies, for any type of biosimilar switching or substitution. Each country's authorities make their own decision about what drugs are available, in some cases mandating large scale switches from originators to biosimilars.<sup>24</sup> These switches have shown no evidence of any changes in clinical outcomes.<sup>25</sup> Canada has also been adopting economically-driven large scale switching, beginning with a major private plan (Green Shield Canada), followed by several of the country's largest provinces.<sup>26</sup> Tenders—formal procedures to purchase medications using competitive bidding—are very common in Europe but increasingly not 'winner takes all,' and more than one product is available to support the sustainability of the market, as we discuss below. Patients will be switched to whatever product is available but usually by the prescriber and not a pharmacist.

The existence of the *interchangeability* designation in the U.S. has been said to play a role in creating a perception that any biosimilars that do not receive the designation are different and potentially inferior in comparison to reference biologics.<sup>27</sup> Much of the perception in the U.S. is based on the use of the term *interchangeable*, which has both a lay and regulatory meaning. The lack of an *interchangeable* designation thus connotes in lay person's understanding a lack of safe switching or interchangeability. This understanding is inconsistent with the requirement that an approved biosimilar has no clinically meaningful differences from the originator product and ignores the fact that there is inherent batch-to-batch variability in biologic products.

With mounting evidence on lack of adverse health outcomes from switching, U.S. legislators could revisit the need for the designation. In the absence of statutory changes, the FDA could continue providing more flexibility in granting this designation. The FDA issued draft guidance in 2019 stipulating that, under certain circumstances, a comparative clinical immunogenicity study would not be necessary for approval of certain proposed biosimilar and *interchangeable* insulin products.<sup>28</sup> The FDA could review evidence and issue guidance offering similar flexibility on the requirements to demonstrate interchangeability for a broader range of biosimilar categories.

### *Consistent nonproprietary names*

Although biologic drugs are known widely by their branded, proprietary names, they also carry nonproprietary names that are used internationally, known as international nonproprietary names (INNs). These refer to the active ingredient in the medicine as decided by an expert committee and issued by the World Health Organization (WHO). Biosimilars and their reference products share the same INN as a way to communicate that they have the same active ingredient. In Europe, there are no

differences in nonproprietary names between reference products and their biosimilars. As a result, for example, both the drug Remicade and its biosimilar, Inflectra, carry the same nonproprietary name, infliximab.

The FDA followed the same system for all drugs and most biologics until biosimilars were approved. For biosimilars, the FDA took a different approach with nonproprietary naming, assigning four-letter suffixes to the end of the nonproprietary name, and subsequently generalized this approach to all new originator biologics. Thus, in the U.S., Inflectra is known as infliximab-dyyb. These distinguishing suffixes, now “devoid of meaning and composed of four lowercase letters,” as the FDA describes them,<sup>29</sup> are not replicated on the original reference product side; in other words, Remicade is simply infliximab, with no suffix. FDA noted that its motivation was to permit monitoring of biosimilars in post-market surveillance systems.<sup>30</sup> As noted above, such RWE in Europe has been helpful for confirming the clinical equivalence of biosimilars. However, various stakeholders have suggested that this policy of differential naming inadvertently creates the impression that biosimilars are inferior, sowing mistrust among clinicians,<sup>31</sup> and potentially limiting clinical uptake.

To address the potentially negative implications of its biosimilars naming policy, the FDA could apply its naming strategy to all biologic products, including existing originators, reversing its most recent naming guidance.<sup>32</sup> Should FDA decide to abandon the suffixes altogether, the Centers for Medicare and Medicaid Services (CMS) would need to implement distinct identifiers in its claims processing for originator biologics and biosimilars—akin to National Drug Codes (NDCs) used in Part D claims. These perception issues arising from the FDA’s existing naming policy could also be addressed through the education and awareness activities described below.

## Intellectual Property Issues

The role of intellectual property protections in affording drug developers with temporary monopolies has been central to the pace of entry into the specialty market for biosimilars. In the U.S. in particular, manufacturers of reference products have filed for and obtained large numbers of patents, resulting in “patent thickets” that delay market entry of biosimilars well beyond the standard twenty years of patent protection (see Humira case study at right). By contrast, the European Patent Office (EPO) and individual European countries, including their courts, have taken specific steps to limit patent thickets, as described below.

### *Scrutinizing “prior art”*

The laws of most countries require similar demonstrations of novelty and “non-obviousness,” or inventiveness, before a product can be awarded a patent. Prior art is any evidence that an invention is

### **Humira: a case study in patent thickets**

Since the mid-1990s, the manufacturer of Humira, a biologic that treats symptoms of various inflammatory conditions such as Crohn’s disease, filed 76 applications with the European Patent Office and 63 applications in Japan.

In contrast, the same manufacturer has filed 247 applications with the U.S. Patent and Trademark Office. Eighty-nine percent of Humira’s U.S. patents were filed after the drug already obtained its U.S. marketing approval. Nearly fifty percent of the applications in the U.S. were filed more than 20 years after the initial scientific research began and more than a decade after the product was first marketed.

Source: <https://www.i-mak.org/humira/>

already known, and that “someone, somewhere, sometime previously has described or shown or made something that contains a use of technology that is very similar to your invention.”<sup>33</sup> There are subtle differences in the way the EPO and the U.S. Patent and Trademark Office (USPTO) approach prior art that mean that certain patent claims are accepted by the USPTO that would be denied by European countries—thus contributing to formation of patent thickets.<sup>34</sup>

For example, patent applications at the EPO are reviewed by three patent examiners rather than just one at the USPTO.<sup>35</sup> The EPO tends to search more aggressively than the USPTO to find evidence that an invention is already publicly known before a patent application’s filing date.<sup>36</sup> The U.S. also permits applicants to make their inventions publicly known up to one year before filing a patent application without being deprived of their patent rights, whereas such disclosures would generally constitute prior art in Europe.<sup>37</sup> To address these differences, the USPTO could take a more rigorous approach to patent examination upfront to deny parts of the patent thicket that are likely rejected in Europe. The FDA could assist by providing information about the originator biologic’s manufacturing processes to the USPTO to help it ensure that late-stage manufacturing process patent applications do not improperly thwart competition.<sup>38</sup>

#### *Approaches to double patenting*

In most European national patent systems, it is an accepted principle that two patents cannot be granted to the same applicant for one invention with the same effective filing date. The EPO takes a narrower approach than the U.S.<sup>39</sup> and allows double patenting only in limited cases in which there is substantial overlap between the patent claims, but not when the claimed subject matter is the same.<sup>40</sup> By contrast, U.S. patent holders can file “continuation” applications—new patent applications that put forward additional claims based upon the same description and priority date(s) as a pending “parent” application. If granted, these applications can result in extending a patent’s breadth, and thus the number of patents on the original reference product that any biosimilar manufacturer will have to address in the event of litigation.

To address this issue, the USPTO could limit the number of continuation applications that a patent holder may file. Reflecting this approach, a final rule from the George W. Bush Administration in 2007 sought to limit an inventor to filing only two new continuing applications per application family.<sup>41</sup> That rule was rescinded by the Obama Administration in 2009 and never came into effect, but a similar approach could be proposed again, although it might require a legislative change in light of a 2009 Federal Circuit case finding that this provision of the final rule was inconsistent with the law.<sup>42</sup>

#### *Shorter regulatory exclusivity*

In addition to patent exclusivity as a form of temporary monopoly protection for drug developers, regulatory exclusivity may be granted as well. Regulatory exclusivity exists in two forms: 1) data exclusivity during which the regulatory agency will not accept an application for a competitor product that relies on safety and effectiveness data from a reference product, and 2) market exclusivity, during which the regulator will not approve a follow-on product’s application.<sup>43</sup>

The U.S. has the longest regulatory exclusivity period for biologics, with the BPCIA granting 12 years of exclusivity. In contrast, the exclusivity period for biologics is 10 years in the EU, 8 years in Canada and



Japan, and 5 years in Australia and New Zealand. The U.S. exclusivity period has been hotly debated, with supporters of longer exclusivity period emphasizing incentives for innovation, against arguments for greater affordability. It is notable that the 10-year exclusivity term in the EU, which applies to drugs as well as biologics, can be extended for a year for a new indication that requires clinical data.

Decreasing the regulatory exclusivity period may not have a significant impact in the U.S. given the existence of patent thickets, which often extend monopoly protection well beyond the 12-year period of regulatory exclusivity.<sup>44</sup> Nonetheless, if patent thickets are addressed by policymakers, shortening the period of regulatory exclusivity could also help speed new biosimilars onto the market.

## Pricing and Reimbursement Issues

There is broad recognition in the United States and Europe that pricing and reimbursement considerations are key to biosimilar adoption. A key distinction between European systems and the U.S. is the different degree and nature of government involvement in price negotiation and the regulation of the payers' market. The approaches also differ among European countries.

Some of the key pricing mechanisms used in European countries are pricing the biosimilar at a specified percentage below the price of the originator and using a maximum price that is set by external (international) reference pricing. Other mechanisms include allowing manufacturers to charge prices of their choosing when products are launched, and using internal reference pricing that sets a uniform reimbursement level for both an originator reference product and its biosimilars. In most European countries, multiple pricing mechanisms are combined to determine the price of the biosimilar (for example, pricing the biosimilar at a certain percentage below the price of the originator, while also setting an external reference pricing ceiling).<sup>45</sup>

In the U.S., reimbursement is heavily influenced by Medicare policy. Most biologics are physician-administered drugs that are reimbursed as a medical benefit (Medicare Part B). Reimbursement of the originator set at 106 percent of its average sales price to providers (functionally 104.3 percent due to sequestration, and the average sales price is calculated with a lag). Reimbursement of each biosimilar is set equal to its own average sales price plus 6 percent of the originator sales price. Equalizing the add-on payment is intended to limit physician incentives to prescribe the higher-priced drug. Generally, the biosimilar payments are significantly lower than the originator payments because the prices are lower. As we describe below, unlike Medicare, some commercial plans have implemented preferred reimbursement for certain biosimilars,<sup>46</sup> along with utilization management programs, as in pharmacy benefit management programs.

Although national healthcare systems are structurally different, the European experience offers some lessons applicable to the U.S. in the realm of pricing, financial incentives to providers, and patient cost-sharing involving biosimilars.

### *Incentivizing providers to adopt biosimilars*

As with other medical products, provider incentives can influence the use of biologics and biosimilars. A key tool for encouraging the use of lower-priced medicines in Europe is internal reference pricing. (Note

that this is different from international reference pricing.) Under this mechanism, medicines that are considered interchangeable are clustered into a reference group and reimbursed based on a uniform price.<sup>47</sup> Research that surveyed policies on biosimilars in 24 countries—20 EU Member States, plus Iceland, Norway, Russia, and Serbia—found that in two thirds of them, the originator biologic and its biosimilars are subject to internal reference pricing.<sup>48</sup> Setting the same reimbursement levels for originators and biosimilars is a much stronger incentive to shift to lower-cost biosimilars than the existing status quo in Medicare and most other U.S. insurance plans, where the payment rates are specific to each product.

European countries have also issued biosimilar prescription targets to physicians and sometimes coupled them with financial incentives to encourage physicians' prescription of biosimilars. For example:

- In the United Kingdom (UK), specific prescribing targets and bonuses encourage biosimilar uptake among physicians participating in a National Health Service (NHS) quality-improvement scheme. Providers who adopt 90% best value generics/biologics for new patients within one-quarter of guidance being available, and 80% in existing patients within one year of the of guidance being available, receive an incentive of 1% of contract value for high-cost drugs. In addition, local Clinical Commissioners Groups (CCGs) have entered gainsharing arrangements with providers, allowing them to earn a share of the cost savings achieved by prescribing biosimilars, as in the case of the South West London Medicines Optimization group following the launch of the first rituximab biosimilar.<sup>49</sup>
- In France, shared savings or “gainsharing” arrangements between hospitals and the branch of Social Security that pays medical costs have been recently rolled out for three molecules: adalimumab, insulin glargine, and etanercept. Under these arrangements, hospitals receive 20-30 percent of the savings off of reference product prices for each biosimilar prescription. Early results demonstrate a higher initiation rate on biosimilars for adalimumab and insulin glargine, and a growth in the penetration rate, compared to control groups that did not partake in the gainsharing experiment.<sup>50</sup>
- In Germany, gainsharing arrangements have been put in place to drive physicians' biosimilar use. One regional physician group and one payer, for example, have agreed to split the savings derived by using infliximab for patients with ulcerative colitis or Crohn's disease in place of Remicade. These arrangements, negotiated on a regional level, have contributed to the high uptake of biosimilars in the country.<sup>51</sup>

Based on this experience, several approaches could enhance the adoption of biosimilars in Medicare Part B:

- Adopt a single payment rate for biosimilars and their reference biologic<sup>52</sup> in one of the following ways:
  - Pay all these products the same rate based on the volume weighted-average payments for all products in the group.<sup>53</sup> This would be in contrast to the CMS payment policy that was in place before 2018 that only grouped the biosimilars of the same reference product, but not the reference product itself, under the same reimbursement.<sup>54</sup> Alternatively, payment could be based on a blended rate for each biosimilar and the originator that partly reflects its own price and partly the prices of the other products in the group.

- Alternatively, to create even more vigorous price competition, CMS could reimburse all products in the group for the least costly alternative (LCA), that is, based on the ASP of the lowest-cost product in the group.<sup>55</sup> CMS had used the LCA reimbursement methodology in the past for clinically similar drugs, but it later discontinued it in response to a court ruling.<sup>56</sup>

CMS may need Congressional authority to implement either of these options on a national basis.

- Based on the European experience, and analogous payment reforms for other services in the U.S., there are other, alternative, pathways for enabling providers to share in the savings from adopting biosimilar products:
  - Shared Savings—Providers potentially already have incentives to use lower-cost biosimilars through shared savings in accountable care organizations (ACOs) and episode-based payment models (e.g., for cancer care) and increasing the uptake of these models could help increase the use of biosimilars. The CMS Innovation Center (CMMI) could also implement a biosimilar-specific shared savings program to further encourage their uptake by providers, allowing participating providers to share in some of the Medicare savings when they choose biosimilars over originators (such as by granting them a fixed payment or a percentage of the difference in ASP between the biosimilar and the reference product),<sup>57</sup> to align provider incentives with the goal of reducing drug costs in Part B.
  - ASP add-on increase – Some recent Congressional proposals would increase the ASP add-on for biosimilars to 8% of the originator’s ASP.<sup>58</sup> As noted above, payment to providers for biosimilars is currently based on the biosimilar’s ASP plus an add-on fee that is based on the ASP of the originator.

### *Patient cost-sharing and biosimilar use*

Around the world, stakeholders have emphasized the importance of patient cost-sharing, its role in driving utilization, and its direct relationship with biosimilar uptake. European stakeholders have noted that while the outpatient biosimilar market in Europe is not as developed as the hospital market, it tends to be more developed where there are positive patient incentives in the form of reduced copayments.

Across Europe, payers have taken different approaches to patient cost-sharing. For example, in conjunction with internal reference pricing arrangements, countries have adopted copayment policies that favor the use of lower-cost biosimilars. These approaches exist in different variations and require that patients pay the difference between the retail price of the product of their choice and the reference reimbursement price, or the price difference between the originator and the biosimilar. These policies exist in Germany, Poland, Spain and Sweden,<sup>59</sup> and a similar proposal was recently introduced in France. In Hungary,<sup>60</sup> higher copays are charged to ‘non-preferred’ drugs, e.g., originator biologics. Some German Sick Funds, the nonprofit entities that cover most of the population, have adopted zero

copayments for preferred anti-inflammation Tumor Necrosis Factor biologics to encourage their uptake.<sup>61</sup>

In the U.S., some commercial plans have adopted similar strategies, with preferential coverage or lower out-of-pocket payments for lower cost biosimilars. However, many plans have given preferential coverage to the originator, so that the biosimilar's cost-sharing may not be lower than the originator biologic's cost-sharing. In addition, some plans require beneficiaries to try the originator before gaining access to the biosimilar, in line with the plan's formulary preferences.<sup>62</sup> These coverage policies are related to rebate arrangements with the originator, and have been observed in some European cases as well. As we describe in the next section, even if such rebates result in lower net costs in the short term, they can complicate the development of a robust biosimilar market.

### *Rebates and short- and long-term savings*

With more biosimilar purchasing experience, some European countries have concluded that short-term savings resulting from purchasing mechanisms that exert maximum pressure on prices, such as national tenders that select a single supplier based on net price after rebates, risk the long-term sustainability of the biosimilars market. Countries such as the UK<sup>63</sup> and Denmark<sup>64</sup> are moving away from awarding all contracts to a single supplier (so called "winner-takes-all" contracts), supporting the sustainability of the biosimilars market and promoting competition by keep multiple entrants in the market concurrently.

However, unless afforded winner-takes-all contracts, biosimilars need to compete for market share against originators. In that context, originator use of exclusive contracts with "loyalty rebates" – that is, larger rebates linked to retaining a large share of market sales – has raised concerns about anticompetitive conduct in Europe. In particular, the UK's Competition and Markets Authority (CMA) investigated a loyalty rebate scheme that linked the level of discount offered on a drug to the total amount of the drug purchased, in an attempt to dissuade the NHS from adopting biosimilars, regardless of the potential savings.<sup>65</sup> CMA found that the scheme was designed "to have an exclusionary effect by making entry more difficult and the criteria and rules (...) demonstrated its potential to have an exclusionary effect."<sup>66</sup> While CMA eventually closed the case because the attempt was ultimately not executed as designed, it signaled its concern about such conduct.<sup>67</sup>

In the U.S., contractual agreements between manufacturers and healthcare system participants provide short-term incentives that can be challenging for biosimilar entry. In particular, biosimilars commonly face an obstacle in gaining market share because a manufacturer with a large market share and existing preferential formulary placement effectively offers a total rebate that the entrant cannot match unless the entrant's discount, coupled with restrictions on continued prescribing of the originator, are substantial enough to switch most or all the patients to the new drug. For all of the regulatory reasons described above, U.S. stakeholders have limited ability and appetite to undertake such rapid and large-scale shifts.

The large share-based rebates for originator drugs have important implications for the growth and sustainability of the biosimilars market in the United States. U.S. payers could consider longer-term contracts that do not rely exclusively on short-term rebates to enable more entry and thus more long-term price competition (long-term contracts involving hospitals and generic drug manufacturers have brought more long-term competition into some previously unstable generic drug markets). In addition

to changes in payments that could encourage biosimilar uptake, antitrust scrutiny of exclusionary contracts may be appropriate.

## Education and Awareness Issues

FDA-approved biosimilars are required to be highly similar to reference products, that is, FDA has determined that they have no clinically meaningful differences from their reference biologic.<sup>68</sup> Yet, perceptions remain that clinically meaningful differences exist between originators and biosimilars in both the United States and in Europe.<sup>69</sup> According to a recent survey evaluating perceptions of biosimilars among U.S. rheumatologists, most physicians are hesitant to switch patients from the reference product to the biosimilar when the patient is doing well on the reference product, but they are more likely to initiate biosimilar treatment for treatment-naïve patients.<sup>70</sup> Yet as noted above, no major safety or effectiveness differences between originators and biosimilars have been demonstrated.

The EMA, individual European country regulators, and other stakeholders such as provider associations, realized early on that both physician and patient perceptions of the safety and efficacy of biosimilars could greatly affect their use. As a result, European efforts to address these perceptions have spanned various approaches, including multi-stakeholder-, physician-, pharmacist- and patient-level education. For example, the European Commission and the EMA convene stakeholders annually from different industries and political scopes, focusing on different areas related to biosimilars, including aligning on science-based messaging and addressing misinformation on biosimilars.<sup>71</sup> The EMA also published a patient-focused video in multiple languages that explains how biosimilars are as safe and effective as their reference biologics as well as the EMA's approach to regulating them.<sup>72</sup>

In Norway, the Norwegian Hospital Procurement Trust, Division Pharmaceuticals holds seminars each year for physicians at hospitals to educate physicians on biosimilar prescribing and usage.<sup>73</sup> In the UK, in 2015, the NHS issued a biosimilar guide for physicians highlighting the safety and effectiveness of these products. The National Institute for Health Care and Excellence (NICE) also published case studies aimed at physicians that detailed successes of biosimilars introduction within the NHS.<sup>74</sup>

In the U.S., the FDA and FTC held a joint public workshop in 2020 to discuss reasons for the limited biosimilar uptake in the U.S.<sup>75</sup> At the meeting, biosimilar manufacturers highlighted current misinformation and disparagement of biosimilars by originator companies, and described opportunities to increase adoption by increasing education among stakeholders.<sup>76</sup> FDA recently began producing educational materials for providers<sup>77</sup> and patients<sup>78</sup> that seek to provide objective information on these products and include videos, fact sheets and infographics that discuss the basics and benefits of biosimilars and their development and approval process.

Expanding unbiased education efforts<sup>79</sup> can build physicians' and patients' confidence in biosimilars. There are also important educational opportunities for healthcare professional societies and patient advocacy groups. Congress recently enacted legislation that directs the Secretary of the Department of Health and Human Services (HHS) to create a website that explains the standards FDA uses to review biologics and biosimilars, to help address clinician and patient misperceptions about biosimilars.<sup>80</sup> Payers could support these efforts by sharing such information with prescribers and patients, and by providing data to enable more comprehensive monitoring of outcomes following patient switches from a reference product to a biosimilar.

Payers can also offer educational opportunities for prescribers. Monitoring and evaluating outcomes after a patient switches from a reference product to a biosimilar using data from Medicare and other payers could help to alleviate patients' and providers' concerns. And because private payers make decisions about biosimilars in product formularies and reimbursement, they themselves could be educated on the safety and efficacy of biosimilars. FDA could play a role as well by ensuring that the information payers use is standardized and updated appropriately.

Kaiser Permanente is one example of a payer that has developed effective educational approaches to foster more use of biosimilars. Kaiser has successfully switched a large share of its beneficiaries to biosimilars from to originator products, in part by generating its own real-world data regarding the biosimilars' performance. Based on the analysis, the chiefs of all of Kaiser's relevant medical specialties endorsed the change; educational materials and clinical guidelines were produced for Kaiser's frontline providers, who then launched successful conversations with their patients about switching to biosimilars.<sup>81</sup>

## Conclusion and recommendations

Although health policies abroad have been developed and applied in contexts different from the U.S., there are substantial opportunities for the U.S. to learn from other nations' experiences with practices that have advanced the use of biosimilars. European and American policies on biosimilars have the same goal: lowering the cost of effective biologics after exclusivity for the originator product has expired, while assuring that the available biologics have no meaningful clinical differences. In European markets, biosimilars have achieved more widespread use without evidence of unusual or unexpected adverse events or evidence of differences in effectiveness between biosimilars and their reference biologics.<sup>82</sup>

The following policy implications for the U.S. are informed by the European policies that supported the uptake of biosimilars as part of a growing multisource specialty marketplace.

### *Regulatory*

1. In comparison to the U.S., regulatory agencies abroad, such as the European Medicines Agency (EMA), have adopted more flexible approval processes for biosimilars, limiting requirements for approval when not needed to assure that biosimilars match the safety and effectiveness profile of the originator biologic. These include comparative efficacy trials that compare the safety and efficacy of biosimilars with their reference products in a head-to-head study with U.S.-sourced reference product, particularly for biosimilars with less complex manufacturing processes and those with extensive European experience. In an effort to **reduce unnecessary costs and speed product approvals, FDA could take further steps to streamline the biosimilar development and approval pathway based on growing global experience.**
2. In contrast to European nations, the U.S. requires more substantial clinical studies beyond biosimilar approval to demonstrate interchangeability. These additional requirements include studies that examine the effect of substituting biosimilars for reference products, or switching patients back and forth between them. Moreover, only the U.S. has a specific requirement set by law for determining "interchangeability" of specific biosimilar products and identifying them as such. **U.S policymakers could consider alternative science-based options to the current**



**definition of “interchangeability” and the requirements for demonstrating it to promote substitution of safe and effective biosimilars, including eliminating the statutory designation.**

3. Other countries use the same international nonproprietary name (INN) for both biosimilars and reference products, and the FDA concurred with this in a formal submission to WHO in 2006. Subsequently, the U.S. developed a more complicated nonproprietary naming convention that may lead to misperceptions about the safety and effectiveness of biosimilars in comparison to originators. Along with adopting an alternative approach to tracking particular biologics to develop further RWE, the **FDA could revisit its approach to create a level playing field for both originators and biosimilars.**

#### *Intellectual property*

4. Patent application reviews aimed at determining “prior art”—evidence that an invention or innovation was already publicly known or available before the application was filed—are more robust in Europe than in the U.S. This process limits the issuance of patents of questionable validity. **The U. S. Patent and Trademark Office (USPTO) could conduct similar reviews that would likely result in the denial of many patents that are often used to create a “patent thicket” that creates hurdles for biosimilar entry.**
5. Unlike patent holders in Europe, U.S. patent holders can file “continuation” applications which, if granted, result in extending a patent’s breadth, increasing the number of patents on the original reference product that any biosimilar manufacturer will have to address in the event of litigation. To address this issue, **the USPTO could limit the number of continuation applications that a patent holder may file**, perhaps by revisiting a now-rescinded 2007 rule limiting an inventor to filing only two new continuing applications per application family.

#### *Payment*

6. Multiple European countries set a uniform payment level for original reference products and their biosimilars that promotes the use of the lower-cost biosimilars. **Congress could direct CMS to adopt a similar approach in Medicare Part B by using a single payment rate for all biosimilars and the reference product itself based on the weighted average of their prices, or by using a blended rate for each biosimilar and the originator that partly reflects its own price and partly the prices of the other products.**
7. **Because biosimilars are generally reimbursed through providers, CMS and private payers could expand shared savings arrangements that grant providers a portion of savings from choosing lower-cost biosimilars**, similar to the gainsharing arrangements that have been successfully implemented in some European markets and some alternative payment models in the U.S.

#### *Education*

8. **The FDA and CMS could undertake more multi-stakeholder communication to build awareness of biosimilars and provide objective information about their cost savings, safety, and effectiveness**, building on existing FDA educational activities and using insights from initiatives

implemented in Europe. Key opinion leaders such as professional schools, societies, and physician organizations could adopt reinforcing educational strategies.

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## Appendix

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