The US Biosimilar Market: Stunted Growth and Possible Reforms

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In 2010, Congress created an abbreviated application pathway for biosimilars, versions of approved biologics made by different manufacturers. However, as of November 1, 2018, the US Food and Drug Administration (FDA) had approved only 13 biosimilars under this pathway, of which just 6 were available for patients to use. We review the history of US regulation of biologics and identify manufacturing, regulatory, and marketing issues that have limited biosimilar market entry and uptake, concluding with recommendations for reform.

Over the past decade, patients, physicians, and payors have placed increasing hope that biosimilars—versions of approved biologics made by different manufacturers—would help address rising drug prices by promoting a competitive marketplace for drugs that had previously been sold by a single manufacturer. Biologic drugs—which originate from living cells and include hormones, cytokines, clotting factors, and monoclonal antibodies—are the fastest-growing sector of the pharmaceutical market.[1] Between 2008 and 2017, they comprised 22% (68 of 306) of newly approved drugs, an 8% increase over the previous decade. In recent years, the revenue growth of biologics has been over twofold higher than that of small-molecule drugs.[2] Biologics are also among the most expensive drugs, accounting for about 40% of total US pharmaceutical expenditures despite being used by less than 2% of Americans.[3]

Whether biosimilars will be effective in promoting access to existing and emerging biologic therapies, however, remains unclear. In this article, we explore the reasons for this uncertainty. We trace the history of US regulation of biologics, including the creation of the biosimilar pathway under the Biologics Price Competition and Innovation Act; evaluate the number, type, and price of approved biosimilars under the pathway to date; examine manufacturing, regulatory, and marketing challenges hindering biosimilar competition; and compare the US experience with that of other countries. We conclude by recommending steps that the federal government and states can take to bolster the biosimilar market in the near-term.

US REGULATION OF BIOLOGICS

Federal oversight of biologics began in 1902 with the Biologics Control Act (**Figure 1**).[4] Passed in the wake of public health tragedies in which tetanus-contaminated diphtheria antitoxin killed 22 children,[5] the Act mandated licensure of manufacturers of "viruses, serums, toxins, and analogous products" intended for sale in interstate commerce, as well as clear labeling of the contents, expiration date, and manufacturer of such products.[6] Authority to promulgate licensing regulations was vested with a board comprising the surgeon generals of the Army, Navy, and Marine Hospital Service (a precursor of the Public Health Service Commissioned Corps),[6] while inspections of plants were conducted by federal scientists and intended to provide assurance that the products were prepared with appropriate safety and quality checks.

Biologics were not mentioned by either the 1906 Pure Food and Drug Act, which instituted rules about labeling of drugs that included mandated disclosure of certain addictive substances[7] or the 1938 Food, Drug, and Cosmetic Act, which required evaluation of drug safety to be submitted to the US Food and Drug Administration (FDA) prior to approval.[8] However, parts of the latter act were applied to them. The 1944 Public Health Service Act updated the Biologics Control Act, placing biologics under the purview of the new Public Health Service,[9] and in 1972—a decade after the Kefauver-Harris Amendments created a new formal mandate for preapproval assessments of drug efficacy[10]—biologic stewardship was transferred to the FDA.[5] The centers within the modern agency that bear primary responsibility for approval and postapproval oversight of biologics are the Center for Biologics Evaluation and Research (CBER), which oversees allergenic extracts, blood and plasma products, gene therapies, and vaccines; and the Center for Drug Evaluation and Research (CDER), which regulates cytokines, growth factors, monoclonal antibodies, and immunomodulators.[11]

FROM THE HATCH-WAXMAN ACT TO THE BIOLOGICS PRICE COMPETITION AND INNOVATION ACT

After the Kefauver-Harris Amendments, there was little new policymaking relating to biologics because few existed.[12] Perhaps for this reason, when Congress passed the Hatch-Waxman Act

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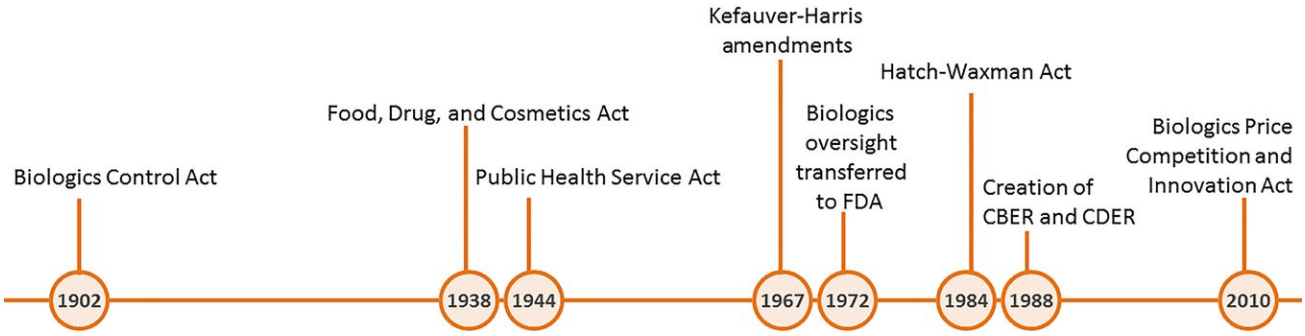

Figure 1 Major events in US regulation of biologics. CBER, Center for Biologics Evaluation and Research; CDER, Center for Drug Evaluation and Research; FDA, US Food and Drug Administration.

in 1984 to create an abbreviated application pathway for versions of approved drugs made by different manufacturers, it applied to small-molecule drugs and not biologics. The pathway allowed a generic manufacturer to earn approval of its version of an approved drug by showing that both drugs had the same active ingredient, dosage form, and strength, as well as the same absorption of the active ingredient at its target site.[13] This eliminated the need for generic manufacturers to recreate the costly clinical trials that might otherwise be required to show safety and efficacy.

The Hatch-Waxman Act was instrumental in bringing generic drugs to market, leading to dramatic growth in the generic drug industry. Whereas only 19% of all prescriptions were dispensed with a generic in 1984,[14] 89% are today.[15] In the intervening years, experience and numerous clinical studies supported the utility of the Hatch-Waxman system in making safe and effective generic drugs available to patients and physicians. Competition spurred by these drugs and state laws that authorize or mandate pharmacists to substitute the FDA-approved generics for brand-name drugs have helped reduce prices of many small-molecule drugs by 80% or more. One government calculation found that generics saved the US healthcare system over a trillion dollars in the last decade.[16]

Although biologics were generally not eligible for the Hatch-Waxman Act's abbreviated generic drug application pathway, biologic manufacturers could use another abbreviated pathway created by the Act: the 505(b)(2) pathway.[17] This pathway allowed manufacturers to rely upon some data used to approve similar but not bioequivalent drugs, thereby reducing the need for some clinical testing. However, drugs approved via the 505(b)(2) pathway were new drugs, not generics and thus, not subject to the effective competition that arose from state drug product selection laws and automatic substitution at the pharmacy. After 1984, a small number of well-characterized biologics that had been approved by the CDER, including calcitonin, human growth hormone, and insulin products, were followed by similar products approved via the 505(b)(2) pathway.[18] However, unlike generic drugs, approval of these products rarely led to meaningful price reductions.[19] In addition, following the 505(b)(2) approval of a version of the human growth hormone somatropin in 2006, the FDA cautioned that similar approval of versions of most biologics would require new legislation.[20]

Such legislation followed 4 years later. By 2010, the clinical and economic imperative for a dedicated, abbreviated application pathway for biosimilars had become more pressing, as more biologics were being approved by the FDA and being sold at high prices. Some of the earliest blockbuster biologics, such as epoetin alfa for anemia, had been on the market for over 2 decades but remained extremely expensive despite expiration of their original patents and other exclusivities.[21] These high prices were experienced as out-of-pocket costs and growing premiums by patients with private insurance, and were helping strain the budgets of public payors, such as Medicaid.

Passed as part of the Patient Protection and Affordable Care Act in 2010, the Biologics Price Competition and Innovation Act created an abbreviated application pathway for biosimilars that was modeled after the Hatch-Waxman Act.[22] However, Congress did not simply replicate the Hatch-Waxman Act's process because biologics are in general more complex than small-molecule drugs. As a result, it could be more difficult to predict how biologics would function on the basis of bioequivalence studies alone. Instead, the Biologics Price Competition and Innovation Act created a new process that allowed the FDA to approve a biologic product based on less than a full complement of preclinical and clinical data if the sponsor could provide analytic studies showing its product was "highly similar" to an approved product, animal studies, and a clinical study or studies demonstrating "safety, purity, and potency" for a use for which the approved product was licensed.[22] Two types of biosimilars were specified under the Act: a standard biosimilar product, which has "no clinically meaningful differences" in safety, purity, and potency compared to the approved biologic and an interchangeable product, a biosimilar product that "can be expected to produce the same clinical result as the [approved biologic] in any given patient."[22] The FDA was charged with identifying the amount of clinical testing required to meet these standards, with the expectation that the interchangeable designation would require a higher level of certainty. For example, for biologics administered more than once to a patient, securing the interchangeable designation required an assessment of the risk of safety or diminished efficacy from alternating between the biosimilar and the originator biologic.[22] Thus, the Biologics Price Competition and Innovation Act differed from the Hatch-Waxman Act in that it created a two-tiered system of products and seemed to necessitate a more substantial range of preapproval testing, predominantly analytic studies but also possibly comparative clinical studies. Still, the

Table 1 FDA-approved biosimilars[a]

Biosimilar nonproprietary name	Biosimilar proprietary name	Approval year	Manufacturer	Biosimilar wholesale acquisition cost	Originator proprietary name	Originator wholesale acquisition cost	Savings (%)	Reason not marketed
Adalimumab–adbm	Cyltezo	2017	Boehringer Ingelheim	–	Humira	$4,872.03 40 mg/0.8 mL kit (2×)	–	Patent Litigation
Adalimumab–adaz	Hyrimoz	2018	Sandoz[c]	–	Humira	$4,872.03 40 mg/0.8 mL kit (2×)	–	Patent Settlement
Adalimumab–atto	Amjevita	2016	Amgen	–	Humira	$4,872.03 40 mg/0.8 mL kit (2×)	–	Patent Settlement
Bevacizumab-awwb	Mvasi	2017	Amgen	–	Avastin	$796.94 25 mg/mL	–	Patent Litigation
Epoetin alfa-epbx	Retacrit	2018	Hospira[b]	$330.90 3,000 u/mL (10×)	Epogen	$497.40 3,000 u/mL (10×)	34	
				$1,764.80 40,000 u/mL (4×)	Procrit	$4115.44 40,000u/mL (4×)	57	
Etanercept-szzs	Erelzi	2016	Sandoz[c]	–	Enbrel	$4,872.00 50 mg/mL (4×)	–	Patent Litigation
Filgrastim-sndz	Zarxio	2015	Sandoz[c]	$275.66 300 µg/0.5 mL	Neupogen	$333.70 300 µg/0.5 mL	17	
Filgrastim-aafi	Nivestym	2018	Hospira[b]	$219.00 300 µg/0.5 mL	Neupogen	$333.70 300 µg/0.5 mL	34	
Infliximab-dyyb	Inflectra	2016	Celltrion[d]	$946.28 100 mg	Remicade	$1,167.82 100 mg	19	
Infliximab-abda	Renflexis	2017	Samsung Bioepsis	$753.39 100 mg	Remicade	$1,167.82 100 mg	36	
Infliximab-qbtx	Ixifi	2017	Pfizer	–	Remicade	$1,167.82 100 mg	–	Manufacturer Choice
Pegfilgrastim-jmdb	Fulphila	2018	Mylan	$4,175.00 6 mg/0.6 mL	Neulasta	$6,231.06 6 mg/0.6 mL	33	
Trastuzumab-dkst	Ogivri	2017	Mylan	–	Herceptin	$1,558.42 150 mg	–	Patent Settlement

FDA, US Food and Drug Administration.
[a]Biosimilars approved under the Biologics Price Competition and Innovation Act pathway as of November 1, 2018. Wholesale acquisition costs were obtained from the Redbook.
[b]A subsidiary of Pfizer, Inc.
[c]A subsidiary of Novartis.
[d]Marketed by Pfizer, Inc.

pathway would allow sponsors to earn the FDA's approval without requiring the same level of testing as novel biologic products.

CURRENTLY APPROVED BIOSIMILARS

As of November 1, 2018, the FDA had approved 13 biosimilars under the Biologics Price Competition and Innovation Act pathway (**Table 1**); none were designated interchangeable. Of these biosimilars, seven were versions of the tumor necrosis factor-alpha inhibitors adalimumab, etanercept, and infliximab, and three were versions of the leukocyte growth factors filgrastim and pegfilgrastim. The remaining biosimilars comprised one version each of epoetin, the antivascular endothelial growth factor bevacizumab used in cancer and eye disease, and the immunoglobulin G1 monoclonal antibody trastuzumab used for human epidermal growth factor receptor 2-positive breast cancer.

Seven of these FDA-approved biosimilars, however, had not yet been marketed. Patent litigation was the primary reason and was ongoing in three cases. Genentech, for example, filed suit against Amgen over its biosimilar bevacizumab in October 2017, 1 month after its approval, claiming that its introduction would infringe upon 24 different patents.[23] Litigation settlements had been reached in three other cases. In March 2017, Mylan dropped its legal challenge against two Genentech patents on trastuzumab.[24] Genentech granted Mylan global licenses to market its biosimilar trastuzumab at a future time (the date was not publicly disclosed). In October 2017 and October 2018, respectively, Amgen and Sandoz similarly agreed to delay the US launch of their biosimilar adalimumab products until 2023.[25,26] Notably, the settlements permitted Amgen and Sandoz to market their biosimilars in Europe 5 years earlier, providing AbbVie—the manufacturer of adalimumab—with undisclosed royalties.[27] These products were first made available in October 2018 in Europe, reportedly contributing to price decreases of up to 80% in some countries.[28]

The six biosimilars that were available in the US, by contrast, offered modest savings. As of August 2018, their wholesale acquisition costs were between 17% and 57% less than their originator counterparts. A recent study reported that, in June 2017, the mean out-of-pocket cost of an 8-week prescription of biosimilar infliximab in Medicare Part D plans was 18% less (US $2,185 vs. US $2,667) than originator infliximab.[29] The uptake of marketed biosimilars has

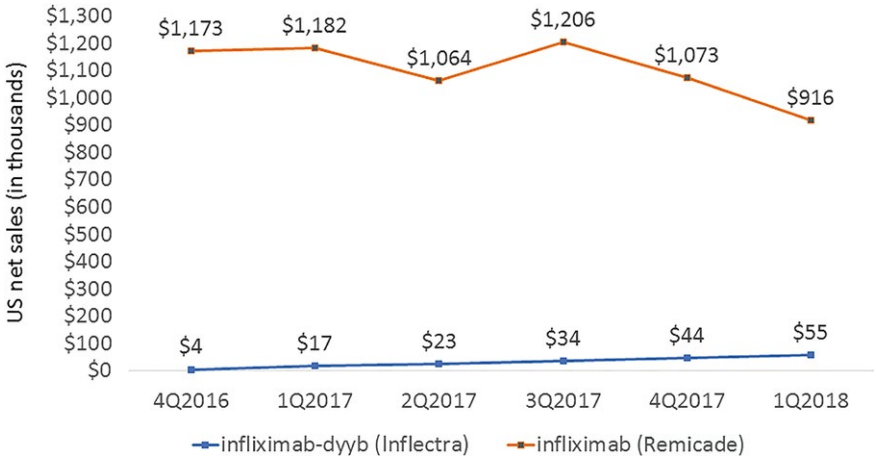

Figure 2 US net sales of infliximab (Remicade) and infliximab-dyyb (Inflectra). Data were obtained from SSR Health. Janssen manufactures infliximab. Celltrion manufactures infliximab-dyyb but Pfizer, Inc. markets it in the US. Between the fourth quarter of 2016 and the first quarter of 2018, net sales of infliximab fell from US $1.173 billion to $916 million, whereas net sales of infliximab increased from $4 million to $55 million.

also varied widely. Sandoz's biosimilar filgrastim has captured about 35% of the US filgrastim market,[30] including 32% of monthly filgrastim use in Medicare Part B in December 2016.[31] By contrast, Celltrion's biosimilar infliximab (marketed by Pfizer, Inc.) accounts for only about 5% of the US infliximab market (**Figure 2**).[30]

Eight years after passage of the Biologics Price Competition and Innovation Act, patients, physicians, payors, and policymakers have been frustrated by the small number of biosimilars approved by the FDA, the smaller number of FDA-approved biosimilars marketed by manufacturers, and the modest uptake and cost-savings characteristics of these marketed biosimilars.[3] Reasons for the disappointing US biosimilar market to date can be traced to manufacturing, regulatory, and marketing issues.

MANUFACTURING ISSUES

Manufacturing biosimilars is more challenging and costly than generics in part because biosimilars are more sensitive to changes in environment,[32] necessitating production, maintenance, and administration under highly specific conditions. The scientific knowledge and technical skill needed to manufacture biosimilars are also specialized[33] and the equipment expensive.[34] Accordingly, the Federal Trade Commission (FTC) estimated in 2009 that it took on average 8–10 years and US $100–$200 million to manufacture a biosimilar, compared to 3–5 years and US $1–$5 million for a generic.[35]

The complicated and costly process for manufacturing biosimilars greatly reduces the number of potential manufacturers that have the technical expertise and market capitalization to make a high-quality product that would pass the FDA's exacting standards. Adding to the high manufacturing barrier to market entry are so-called trade secrets. Defined broadly in legislation adopted by most states as any information that derives value "from not being generally known…and not being readily ascertainable by proper means,"[36] trade secrets cover critical information related to biologic manufacturing processes, such as the choice of cell line, chilling diffusion of knowledge to would-be competitors.[37]

One of the main outcomes of the manufacturing complexities related to biosimilars is that a separate industry of biosimilar manufacturers has not emerged after 2010 in the same way that the international generic drug industry flourished after 1984. Of the eight manufacturers of approved biosimilars in the US, three (Amgen, Boehringer Ingelheim, and Pfizer, Inc.) also manufacture originator biologics and two (Hospira and Sandoz) are subsidiaries of originator biologics manufacturers (Pfizer, Inc. and Novartis). The remaining three biosimilar manufacturers (Celltrion, Mylan, and Samsung Bioepis) each have market capitalizations exceeding most generic manufacturers (**Figure 3**).

REGULATORY ISSUES

Regulatory policies have also contributed to the limited US market for biosimilars. As set forth in the Biologics Price Competition and Innovation Act, initiation of the 351(k) abbreviated biologic application process can include two preliminary steps. The first step is called the "patent dance," in which the biosimilar manufacturer shares its licensing application with the originator manufacturer. In the second step, the biosimilar manufacturer is required to provide notice to the originator manufacturer of its intent to enter the market no later than 180 days before marketing the biosimilar.

The patent dance was intended to facilitate litigation to determine if the biosimilar manufacturer had infringed the originator manufacturer's patents. However, the dance became a barrier to entry for some biosimilar manufacturers. First, the patent dance required biosimilar manufacturers to reveal potentially sensitive manufacturing information to competitor manufacturers, which they may be loath to do, particularly because many of these manufacturers compete in other markets as well. Second, because the dance occurred behind closed doors, originator manufacturers could take steps to delay the dance proceedings, indefinitely putting off when the biosimilar manufacturer might be able to reach the market. Third, as a new procedure, there was no precedent for it. As a result, some biosimilar manufacturers determined that they would rather skip the dance and seek approval for their products,

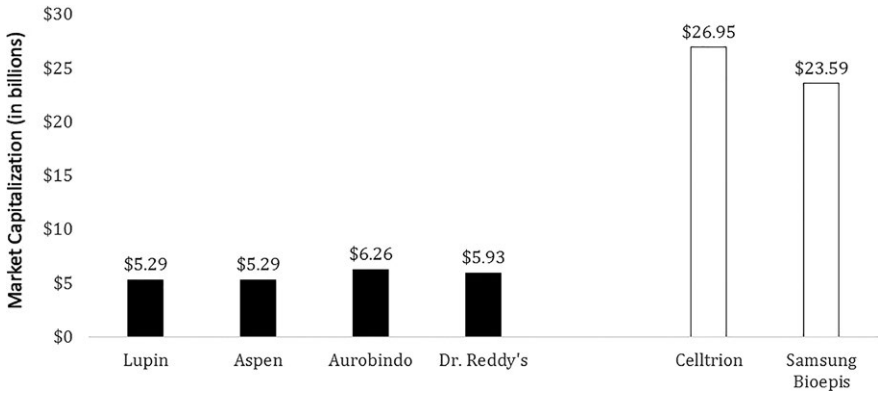

Figure 3 Market capitalization of select generic and biosimilar manufacturers. Data from Bloomberg on November 5, 2018. Black = generic manufacturers; white = biosimilar manufacturers that are not also originator biologic manufacturers or subsidiaries of originator manufacturers.

inviting patent infringement lawsuits and then take their chances in open court—a variant of the well-worn process that originally emerged from the Hatch-Waxman Act. In 2017, the question of whether the patent dance was mandatory reached the US Supreme Court, which ruled that it was not.[38] The Court also examined the requirement for marketing notification, and found that it could occur before FDA approval.[39] About half of currently approved biosimilars have chosen not to start the patent dance.

The FDA's interpretation of testing requirements for biosimilar approval has also posed challenges. Although the Biologics Price Competition and Innovation Act does not mandate comparative clinical studies for biosimilar approval, the FDA has remained concerned—appropriately so—about "residual uncertainty" in biosimilarity,[40] a function of the structural complexity of biologics, their sensitivity to variation in manufacturing processes, and existing analytic limitations. The clinical studies expected of some biosimilar manufacturers follow structural and functional characterization, animal testing, pharmacokinetic and pharmacodynamic analyses, and assessment of potential immune responses (i.e., immunogenicity), and may be similar in size and scope to the pivotal trials conducted to secure approval of the originator biologic. For example, the FDA approved Amgen's filgrastim after a placebo-controlled, phase III trial of 210 patients taking combination chemotherapy for small-cell lung cancer,[41] and Sandoz's biosimilar filgrastim based on a comparative clinical study of 218 patients taking combination chemotherapy for breast cancer.[42] However, the FDA more recently approved Pfizer, Inc.'s biosimilar filgrastim without a comparative clinical study involving the product.[43] Additionally, the FDA permits extrapolation of clinical data across indications if a manufacturer can articulate "sufficient" scientific justification, eliminating the need for multiple, indication-specific trials.[40] Celltrion accordingly secured the FDA approval of its biosimilar infliximab for all indications of the original infliximab (Crohn's disease, ulcerative colitis, rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, and plaque psoriasis) by conducting comparative clinical studies in just rheumatoid arthritis and ankylosing spondylitis.[44]

A final important regulatory issue relates to interchangeable biologics. No biosimilars approved via the Biologics Price Competition and Innovation Act pathway yet carry an interchangeable designation. Concern remains that repeated patient switching between originator and interchangeable biologics could have a "booster" effect, increasing the risk of adverse immune responses.[45] Empirical support for this theory, however, is limited. Several studies have failed to find increased immunogenicity from switching between originator biologics and biosimilars.[46–48] A 58-week equivalence trial—in which 645 patients were initially randomized to receive Abbvie's adalimumab or Boehringer Ingelheim's biosimilar adalimumab and then rerandomized at 24 weeks—reported similar proportions of switched and nonswitched patients with antidrug antibodies and neutralizing antibodies.[49] Additionally, widespread use of biosimilars in the European Union (EU) over the past 12 years—in some cases involving nationwide changes[50]—has been safe, with the European Medicines Agency (EMA) stating that it has not identified "any relevant differences in the nature, severity, or frequency of adverse effects between biosimilar medicines and their reference medicines."[51] To the extent that a switching risk does exist, it is unclear whether it is greater than the risk resulting from variation between different batches of the same biologic. Such variation was associated with several cases of thrombotic microangiopathy with interferon beta,[52] underscoring the importance of rigorous postapproval biologic surveillance and the possible need for interchangeability reassessments over time.

MARKETING ISSUES

Features of the current US pharmaceutical market have hampered uptake of biosimilars. Originator manufacturers often protect their products with multiple patents covering methods of production and use. As with generic manufacturers, responsibility falls to biosimilar manufacturers to challenge these patents in court, which may lead to some of them being invalidated as erroneously granted or being found not to cover the manufacturing process used by the biosimilar manufacturer. In extreme cases, as with the blockbuster drug adalimumab,[53] originator biologics may have dozens of patents that can take several years to litigate. Settlements of patent challenge cases in the small-molecule drug market have delayed entry of generic drugs, and such settlements have arisen in originator biologic/biosimilar manufacturer disputes as well. In three cases thus far, originator manufacturers have settled patent disputes with biosimilar manufacturers, offering something

of value in return for delayed biosimilar entry.[25–27] The Supreme Court has ruled that such settlements are reviewable for antitrust violations by the FTC.[54]

Another problematic strategy that has emerged in the biologic market relates to so-called "rebate traps." Originator manufacturers have tried to curb biosimilar uptake by conditioning rebates on exclusivity of sales. Such rebate traps can make it costlier for an insurer to cover a lower-priced biosimilar if the insurer cannot switch a substantial proportion of its patients taking the originator biologic to the biosimilar.[55]

Finally, biosimilars may face skepticism from physicians and patients. Although few peer-reviewed studies on perceptions of biosimilars exist, a 2014 survey of 81 Canadian rheumatologists found that 72% were unlikely or very unlikely to offer a biologically naive patient a biosimilar over an originator biologic.[56] Skepticism about generic drugs was also high at the time of the Hatch-Waxman Act, and over 30 years later, about a quarter of physicians and patients remain skeptics of generics.[57,58] As skepticism about generic safety and effectiveness has improved over time, so it likely will also for biosimilars after sufficient experience with them.

The FDA's naming policy for biosimilars may help fuel physician and patient skepticism. In 2017, the agency published guidance codifying its intent to add a random four-letter suffix to the nonproprietary name of biologics to help ensure that patients receive the correct product and to facilitate product-specific pharmacovigilance.[59] Although in theory applicable to both originator biologics and biosimilars, these suffixes have in practice only been routinely applied to biosimilars. Notably, FTC staff opposed the policy, noting that "misperception that the drug substance in a biosimilar differs in clinically meaningful ways from that in the reference biologic could deter physicians from prescribing biosimilars, thus impeding the development of biosimilar markets and competition."[60]

INTERNATIONAL EXPERIENCES

The EU was quicker than the US to embrace biosimilars. The EMA approved its first such product under a dedicated, abbreviated approval pathway a decade earlier than the FDA and has since approved 45 other biosimilars, including biosimilar insulin glargine, biosimilar insulin lispro, and multiple biosimilar rituximab products.[61]

In the 18 years that biosimilars have been marketed in the EU, they have had a meaningful impact on drug prices and use. A European Economic Area analysis of granulocyte-colony stimulating factors, human growth hormones, antitumor necrosis factors, fertility agents, epoetins, and insulins found that prices fell between 7% (insulins) and 31% (epoetins) upon introduction of a biosimilar product, whereas use increased between 19% (insulins) and 122% (granulocyte-colony stimulating factors).[62] Another report estimated that biosimilars could save European countries up to €15 billion (about US $25 billion) between 2016 and 2020.[63] The European Union has achieved these outcomes without centralized regulations on interchangeability. The EMA leaves such rulemaking to member states, which have generally not authorized automatic substitution. However, most EU states operate single-payer healthcare systems and, thus, wield considerable influence over which products patients use. Additionally, unlike the FDA, the EMA does not require use of random four-letter suffixes for biosimilar nonproprietary names.

Elsewhere, other countries have aggressively promoted biosimilar development and use. South Korea created an abbreviated approval pathway analogous to the Biologics Price Competition and Innovation Act pathway in 2009[64] and has invested heavily in the biosimilar industry, with a goal of controlling over 20% of the global market for biosimilars by 2020.[65] In 2018, the country was home to 7 biosimilar manufacturers and 12 approved biosimilars. Australia began implementing two biosimilar "uptake drivers," officially encouraging and making easier physician prescribing of biosimilar products over originator products for treatment-naive patients.[66] Additionally, the Australian Pharmaceutical Benefits Advisory Committee recently recommended granting interchangeability status to Amgen and Samsung Bioepis's biosimilar adalimumab products,[67] which would enable pharmacists to automatically substitute them for Abbvie's adalimumab. This recommendation was based on the same comparative clinical studies submitted to the FDA.[68,69] Such developments point toward a growing global market for biosimilars in coming years.

THE FUTURE

The US needs to enhance its biosimilar market for the benefit of patients, physicians, and government healthcare budgets. In June 2018, the FDA offered some pathways to accomplish this goal in its Biosimilar Action Plan.[70] Steps included developing new review tools, such as standardized review templates and models correlating pharmacokinetic and pharmacodynamic testing with clinical outcomes, exploring the feasibility of data sharing agreements with regulators in other countries to enable the use of non–US-licensed products as comparators, and creating a new Office of Therapeutic Biologics and Biosimilars. These measures could help improve the efficiency of bringing biosimilars to market.

The action plan further called for final or revised draft guidance on demonstrating interchangeability and for continued education of healthcare professionals. Without further details, it is unclear how effective these steps will be. In addition, Congress could pass new legislation that would condition the FDA approval of originator biologics on disclosure of manufacturing trade secrets in biologics license applications upon expiration of the 12-year regulatory exclusivity period.[71]

To address regulatory obstacles to biosimilar entry and uptake, the FDA could coordinate with other regulators (e.g., the EMA, Health Canada, and the Australian Therapeutic Goods Administration) to create uniform preapproval study requirements with the ultimate goal of a single application dossier that would be sufficient across all jurisdictions. In the absence of the FDA action on interchangeability, states could modify their drug product selection laws to authorize a state board of pharmacy to determine whether automatic substitution of originator biologics with biosimilars would be appropriate in specific cases. Investment in further scientific studies to resolve lingering questions about the safety of biosimilar switching and the feasibility of interchangeability among biologics is also sorely needed to support the Biologics Price Competition and Innovation Act interchangeable designation.

Several actions could similarly reduce marketing barriers for biosimilars. A process called *inter partes* review, created by the 2011 America Invents Act,[72] could enable faster and less expensive resolution of patent challenges before specialized administrative patent judges,[73] potentially helping to clear "patent thickets."[74] Hospira, for example, used *inter partes* review to invalidate a Genentech patent on bevacizumab in 2016.[75] The following year, Boehringer Ingelheim and Cohereus Biosciences also prevailed in invalidating multiple claims in AbbVie patents on adalimumab.[76,77] In 2018, the Supreme Court upheld the constitutionality of *inter parties* review.[78] Although there is not yet a clear connection between the use of *inter partes* review and earlier entry of biosimilar drugs, the process has the potential to serve as a valuable tool for biosimilar manufacturers. Congressionally mandated reporting of biologic patents in the "Purple Book"—an FDA publication of biologic-specific information—could help spur such *inter partes* challenges, and mandatory disclosure of biologic patent settlements to the FTC could facilitate antitrust enforcement. The latter requirement was included in legislation that passed Congress and was signed by the President in September 2018.[79]

Physician and patient skepticism, meanwhile, could be mitigated by disseminating materials that address outstanding questions about biosimilar safety and effectiveness and by rescinding the current confusing FDA naming policy. Use of such suffixes is not necessary for product-specific surveillance; the Centers for Medicare and Medicaid Services already requires submission of unique national drug codes for reimbursement of all pharmacy-dispensed medications[80] and unique Healthcare Common Procedure Coding System J-codes for reimbursement of physician-administered biosimilars,[81] which can be used in claims-based observational investigations. Finally, enhanced transparency and regulation of prescription drug rebating practices, something the current administration has indicated support for on numerous occasions, could help limit exclusionary dealing.

Without such steps to generate a vibrant biosimilar market in the US, high prices for older biologics will persist, which would be harmful to patients relying on those products and reduce incentives for private investment in the next generation of important treatments. Because the US marketplace was designed to provide manufacturers with self-limited periods of market exclusivity on new pharmaceutical products during which maximum prices could be charged, an alternative model would be to pass federal legislation mandating a price cut for originator biologics after expiration of their key original patents, which could approximate the cost savings anticipated from the availability of biosimilars.[19]

CONCLUSION

Despite the small number of products that have entered the market and their modest cost-savings to date, biosimilars have the potential to play an important role in containing rising US prescription drug prices. To achieve this promise, policymakers must address existing manufacturing, regulatory, and marketing barriers to market entry and uptake, including trade secret protection of critical manufacturing information, preapproval testing requirements, a lack of interchangeability guidance, patent thickets, rebate traps, and physician and patient skepticism. Although some reforms are underway, more can be done to ensure that biologic therapies are accessible to US patients who need them.

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CONFLICT OF INTEREST

The authors declared no competing interests for this work.

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