Breaking Through on Biosimilars

Delivering More-Affordable, Innovative Medicines to America's Patients

The Biosimilars Council
A Division of AAM

Biosimilars Council White Paper

Amgen Exhibit 1086
Amgen v. BMS
IPR2025-00601

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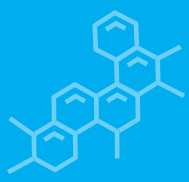
5 **Introduction: The Promise of Biosimilars**
6 Realizing the Potential of Biosimilars
7 **Challenges to Bringing a Biosimilar to Market (Getting In)**
7 Restricted Access to Reference Products
7 Patent Abuses
9 Trade Agreements
10 **Challenges to a Competitive and Viable Long-Term Market for Biosimilars (Staying In)**
10 FDA's Commitment to Biosimilar Development
14 **Reimbursement and Market Access**
14 Changes to Medicare Part B
15 Medicare Part D
16 Exclusionary Contracting Practices and the Rebate Trap
18 **The Patient Perspective**
18 Building the Biosimilars Marketplace: Education and Combatting Misinformation
18 Switching Reference Medicines
20 **Conclusion**
21 **References**

Introduction: The Promise of Biosimilars



The regulatory and legislative landscape for biosimilars will have a significant effect on their success. Policymakers must closely monitor the progress of the biosimilars market and align system incentives to encourage competition and biosimilar development so that America's patients can benefit from these life-saving therapies.

America's patients who suffer from many complex and chronic diseases have promising new treatment options in biologic and specialty medicines. But too often these medicines are extremely expensive, creating challenges to patient access. Now, thanks to biologic medicines known as biosimilars, these advanced treatments are becoming available at a lower cost to millions of patients in the United States living with cancer, rheumatoid arthritis, Crohn's disease, anemia, psoriasis and other conditions.

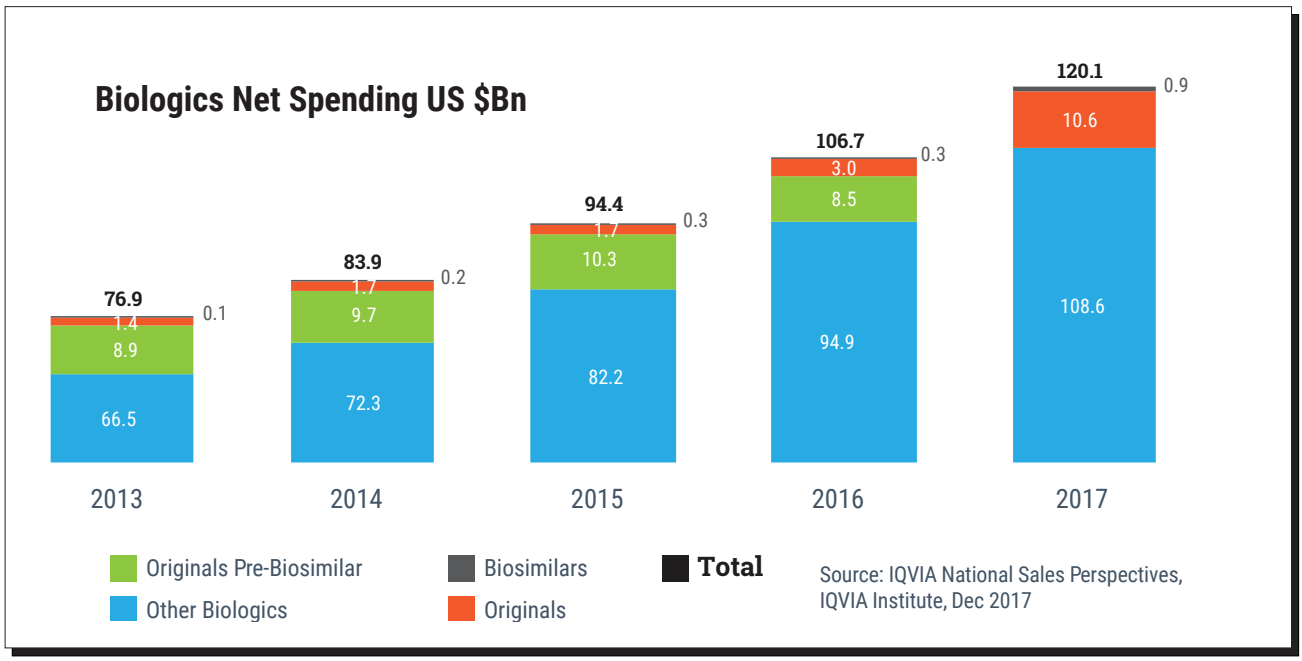
Biologic medicines are produced from living organisms. They are more complex than the chemical compounds that comprise small-molecule drugs. A biosimilar medicine approved by the U.S. Food and Drug Administration (FDA) is subject to the same rigorous standards as FDA-approved biologic medicine referenced by the biosimilar's application (reference product). FDA carefully analyzes each biosimilar compared to its reference product to ensure it has no clinically meaningful differences in safety and efficacy for any given patient. The biosimilar product is analyzed with some of the most sophisticated and innovative pharmaceutical technology available today and assessed by FDA's medical, analytical and statistical experts.

The United States trails Europe in the number of biosimilar approvals and launches: Europe has approved more than 40 biosimilar medicines in the last decade and accumulated more than 700 million patient days of experience with biosimilars. FDA has approved 10 biosimilar medicines and only three of these have been launched on the U.S. market.[1] Some of this disparity in approval numbers can be attributed to the fact that the legislation authorizing FDA to develop an approval pathway was not enacted until 2010, but there are additional factors at play.

For example, the biosimilar medicine development process requires substantially more financial investment. Generic drugs typically cost approximately $5 to $10 million to develop,[2] compared to an average estimated development cost of biosimilars of between $100 and $300 million per product.[3]

Realizing the Potential of Biosimilars

Biologic medicines offer life-saving treatments for patients, but are undeniably costly. While just 2 percent of the U.S. patient population currently uses biologics, they account for 26 percent of national prescription drug spending, a record $453 billion in 2017.[4] Like generic drugs, which saved the U.S. health care system $253 billion dollars in 2016,[5] biosimilars drive competition in the marketplace. Robust biosimilar competition slows the growth of spending and increases access to therapeutic advances that improve the quality and length of patients' lives.



Data from Europe indicate just how much of an impact the presence of biosimilars makes for patients. In fact, patient access to both biosimilars and biologics has increased by as much as 100 percent in Europe as the result of biosimilar availability.[6]

In the U.S., biosimilars will provide greater access to biologic medicines for an additional 1.2 million patients over the next 10 years, according to a study by Avalere Health commissioned by the Association for Accessible Medicine's Biosimilars Council. Women, lower-income and elderly patients will particularly benefit from improved access to lifesaving biosimilar medicines.[7]

It has been estimated that FDA-approved biosimilars could save patients and the health care system anywhere from $54[8] to $250 billion[9] over their first 10 years on the market.

FDA-approved biosimilars are poised to play a vital role in delivering more-affordable treatments to patients, while simultaneously providing much-needed savings to the health care system. Patients, health plans, employers, federal and state governments and other health care stakeholders are counting on these new medicines.

Challenges to Bringing a Biosimilar to Market (Getting In)

Biosimilar manufacturers seeking to launch in the nascent U.S. market face challenges related to scientific development, regulatory approval and manufacturing and production. As market disrupters, they also encounter artificial hurdles intended to thwart competition. Over time a number of specific anti-competitive strategies have emerged as obstacles to development of a robust biosimilars market.

Restricted Access to Reference Products

Some brand-name drug companies block biosimilar competition by creating restricted distribution agreements with distributors that shut out the biosimilar developer from acquiring samples of the reference product. These samples are needed to conduct the scientific analytical comparability tests and clinical trials required to meet FDA's approval standards for biosimilars, which are based on comparing the reference brand biologic product and the biosimilar product.

Bipartisan legislation in the House and Senate, the Creating and Restoring Equal Access to Equivalent Samples (CREATES) Act and the Fair Access for Safe and Timely Generics (FAST) Act, would prohibit branded pharmaceutical companies from restricting access to samples to delay biosimilar competition. The Congressional Budget Office has indicated this legislation would save $3.8 billion over 10 years.[10]

Patent Abuses

Patents are an important element of innovation in drug development and essential to supporting the discovery of new effective treatments to address unmet medical needs. However, the patent system is increasingly being gamed to unfairly prolong a brand-name drug's monopoly and delay patient access to more-affordable, FDA-approved biosimilar medicines. Even though the Biologics Price Competition and Innovation Act of 2009 (BPCIA) gives branded biologic drug manufacturers a 12-year market exclusivity period to ensure a return on investment for new medicines (longer than anywhere else in the world), these patent abuses are proliferating and delay competition.

ADDING NEW, NON-INNOVATIVE PATENTS: PATENT THICKETS

Recent research shows the brand-name pharmaceutical industry is manipulating this system by obtaining dozens of potentially non-innovative patents to extend its market exclusivity farther than policymakers initially intended,[11] a ploy known as building "patent thickets." In these instances, branded biologic manufacturers are attempting to accumulate patents not because they are innovative, but rather to increase litigation and development costs for potential would-be biosimilar competitors. These patent thickets chill competition by discouraging competitors from entering a market because of the exorbitant cost of litigating meritless patents.

AbbVie's Humira® is a glaring example. Humira was first approved in 2002 and treats a variety of disease states including arthritis, plaque psoriasis, ankylosing spondylitis, Crohn's disease and ulcerative colitis.

While Humira has been a boon for patients suffering from these conditions, it can also be prohibitively expensive, at more than $38,000 per year.[12] Although Humira's 12-year statutory market exclusivity expired in 2014 and its principal patent expired in 2016, AbbVie filed more than 75 late-stage patents in the three years prior to the 2016 expiration to delay biosimilar competition. As a result, the last Humira patent won't expire until 2034. While two Humira biosimilar competitors have been approved to date by FDA, none is available to patients. One remains in litigation and the other's manufacturer has settled out of court to mitigate the risk of prolonged, expensive litigation. AbbVie reported net revenues of $12 billion in 2017 for Humira in the U.S. alone, an increase of 18.5 percent over 2016.[13]

This is not an isolated example. Many other brand biologic companies use this tactic of creating "patent thickets" to prevent biosimilar competition. Policymakers should ensure that the patent system and regulatory approval pathway incentivize true innovation, rather than innovative gamesmanship. That means a more stringent review of patents prior to their approval by the Patent and Trademark Office (PTO), as well as economically reasonable and efficient means for competitors to challenge patents that do not meet the necessary legal standards of innovation in the first place.

INTER-PARTES REVIEW PROTECTION

One valuable tool against these patent thickets is an administrative process known as Inter-Partes Review (IPR). Congress established today's IPR process within the PTO as part of the America Invents Act signed into law in 2011.[14] Under IPR, the Patent Trial and Appeal Board (PTAB) at the PTO takes a second look at its earlier decision to grant a patent, and allows third parties to bring evidence about the appropriateness of the PTO's prior decision. The goal of these processes is to "ensure that the poor-quality patents can be weeded out through administrative review rather than costly litigation" and "improve patent quality and limit unnecessary and counterproductive litigation costs."[15]

But the brand pharmaceutical industry is attempting to thwart biosimilar companies' use of the IPR system by challenging their standing to appeal IPR decisions of the patent office.[16] IPRs lend high value to biosimilar companies by providing a more accurate picture of the patent landscape in a timely and less-expensive manner than typical biosimilar litigation. This value is compounded by the ability of the biosimilar manufacturer to file IPRs earlier in the development process so that there is certainty in how to proceed.

The U.S. Supreme Court recently upheld the constitutionality of the IPR process.[17] Successful IPR challenges are more efficient than the patent challenge procedures in court—getting biosimilar drugs into patients' hands faster. However, the brand pharmaceutical industry has worked to weaken this important process despite its many pro-innovation and pro-consumer successes. IPR must be protected to ensure new pharmaceutical patents represent true innovation.

SOVEREIGN IMMUNITY

In a particularly creative effort to protect monopoly prices through patent system abuse, a brand company recently "rented" a Native American tribe's sovereign immunity to shield a patent from the IPR process. In late 2017, the pharmaceutical company Allergan paid millions of dollars to a Native American tribe to take "ownership" of six patents related to its drug Restasis®. In return, the tribe asserted that its sovereign immunity protects the patents from review by the PTO through the IPR process. A recent study found

patients will pay an additional $10.7 billion for Restasis over the next 10 years if these anticompetitive tactics prevent a generic alternative from entering the market.[18]

If brand-name drug and biologic makers know they can shield themselves from PTO's administrative procedures by paying a Native American tribe a small fraction of the amount these pharmaceutical companies receive in revenues each year, this ploy will proliferate. As a result, patients will be denied access to competing biosimilar products as long as invalid patents remain on the books.

The Preserving Access to Cost Effective Drugs (PACED) Act would clarify the authority of the PTO to review patents regardless of sovereign immunity claims that are made to avoid legitimate review of disputed patents.[19]

Trade Agreements

Trade agreements should maintain a balance between the interests of innovation and promoting access to medicine, including the substantial cost savings that biosimilars provide for patients. The inclusion of provisions in trade agreements that would expand brand-name drug company's monopolies and block generic drug and biosimilar competition will harm patient access to more-affordable medicines. Longer marketing or data exclusivity periods or mandates to block competition by extending originator drug company patent terms will delay the growth of the generic and biosimilar markets. Such provisions in internationally binding treaties limit U.S. sovereignty and remove the ability to make changes to U.S. law in the future.

Trade agreements should include incentives to grow the uptake of biosimilar and generic drugs to bring down prescription drug prices. In addition, consistent with U.S. law, our trade agreements should include a strong regulatory review clause that protects the development of biosimilars and generic medicines during the period of patent term for the purposes of developing information to obtain marketing approval from health regulatory authorities.[20] Moreover, trade agreements should require that our trading partners implement a transparent system with a public listing of all patents pertaining to a medicine. Such a system would be facilitated by creation of a public registry of applicable pharmaceutical patents. Trade agreements should also provide effective rewards for the successful challenge of the validity or applicability of a patent. In this way U.S. trade agreements can enhance biosimilar and generic drug competition for the benefit of patients.

Challenges to a Competitive and Viable Long-Term Market for Biosimilars (Staying In)

While biosimilars face significant challenges before even gaining approval, recent developments have demonstrated there are still obstacles to market-based competition once FDA has signed off on an application. Regulatory decisions, payment policy and market incentives all play a critical role in driving patient and provider utilization of biosimilars. These variables will determine the viability of a sustainable biosimilars market in the U.S. If biosimilar manufacturers face barriers to successful market launches, there is risk that investment in biosimilar development will dry up. Without this investment, costly biologics will continue to face little to no future competition, allowing and extending costly biologic manufacturer monopolies.

FDA's Commitment to Biosimilar Development

The BPCIA established and required FDA to implement an abbreviated pathway for biosimilar review and approval. While FDA has made significant progress in the eight years since the law was enacted, there are a number of unresolved issues that affect the viability of biosimilar development.

FDA Commissioner Gottlieb has affirmed the agency's commitment to increasing the efficiency of the biosimilars pathway by developing a Biosimilars Access Plan that will help address some of the current regulatory uncertainty. According to the commissioner, the plan includes "new tools and information resources that can assist biosimilar sponsors in developing high-quality biosimilar and interchangeable products using state-of-the-art analytical techniques. These tools can support…more efficient biosimilar development programs without compromising on our scientific rigor."[21]

By addressing the current regulatory uncertainty that remains in the biosimilars development pathway, FDA can ensure greater efficiency and certainty for biosimilar developers. This in turn will lead to greater patient access, a robust market and significant savings for the health care system.

NAMING

In response to the growing number of biosimilar approvals and increased acceptance of their safety and efficacy, several global regulatory bodies have recently addressed the issue of naming biosimilar products. At the crux of the debate is whether biosimilar medicines must have differentiated technical names. In most countries, biosimilar medicines are required to have a unique brand name.[22] Separate from the brand name, the current global debate has centered on whether to include distinguishable suffixes in the technical naming of biosimilar products. For comparison, traditional generic drugs are identified by a unique name

designated by the World Health Organization (WHO), or International Non-Proprietary Name (INN), that identifies the active ingredient in a drug and is identical to the technical name of the reference product.[23] Because biosimilars are approved by FDA as highly similar to the reference product, and not identical, some have argued for the necessity of a suffix in addition to the biosimilar's INN for purposes of differentiation in prescribing, dispensing and pharmacovigilance.[24] In 2016, FDA adopted the standard of requiring the addition of suffixes to biosimilar products while also adding suffixes to newly approved brand-name biologics.[25] However, so far there is no retrospective addition of suffixes to existing reference products, meaning the reference biologic has only the INN, while biosimilars have the INN plus a suffix, creating an uneven playing field from a prescribing perspective.

Supporters of suffixes cite theoretical safety concerns arising from non-differentiated technical naming. In reality, data from pharmacovigilance systems show that these theoretical concerns have long been addressed by current naming conventions and pharmacovigilance systems.[26] These existing safeguards eliminate the need for unnecessarily complicated and confusing suffixes.[27] Further, investment in awareness and appropriate use of existing pharmacovigilance systems and existing safeguards would create more meaningful assurance than the introduction of complicated, confusing suffixes.

Meanwhile, the use of suffixes can pose a significant barrier to potential adoption of biosimilars. The concept of a different INN is in a way contradictory to the core principles of biosimilarity that ensure absence of clinically relevant differences between the reference and the biosimilar product. Differentiating between a biosimilar and its therapeutically equivalent reference product serves only to create confusion among providers and payors, drawing attention to non-clinically meaningful differentiation, slowing adoption and protecting the brand's market share. FDA should revisit this naming convention to remain consistent with other global regulatory bodies such as the European Union (EU), Australia and the WHO. This will prevent confusion and create the most conducive environment for biosimilar adoption and increased competition.[28]

LABELING

While FDA has yet to issue final guidance on the labeling of biosimilar products, the agency's draft guidance takes important steps toward creating a level playing field between biosimilars and their reference products. Most importantly, it allows biosimilars to rely on its reference product's labeling, which will allow biosimilar manufacturers to effectively compete when promoting their products to providers.[29]

However one aspect of the proposed guidance may cause confusion and undermine the adoption of biosimilar drugs. The guidance calls for biosimilar product labeling to include an explicit statement of biosimilarity.[30] This can be interpreted as an implication that the biosimilar is different in some way from the reference product. By comparison, generic drug products are not required to be labeled as "generics," nor are other complex drugs that are approved based upon reference products required to identify their reference product. Moreover, a statement that the product is a biosimilar does not provide any guidance to a prescribing health care professional.

FDA has attempted to mitigate the potential confusion by proposing an explanatory footnote providing the precise meaning of the term "biosimilar" and the fact that biosimilars have no clinically meaningful differences from their reference product. Nonetheless, the very fact that a product is identified as a biosimilar in the label sends a clear and unmistakable message that it is different, when the only true difference is the regulatory pathway. FDA has acknowledged that use of a footnote is poorly suited to overcoming this confusion.[31] Most worrisome is the potential use of this statement by branded companies to discourage physician prescribing. Because FDA's proposal may inadvertently deter increased competition and patient access to safe, effective and affordable biosimilars, the agency should reconsider requiring a biosimilarity statement on biosimilar labeling.

INTERCHANGEABILITY

An interchangeable product is a biosimilar product that meets additional regulatory criteria to demonstrate it is expected to produce the same clinical result as the reference product in any given patient and that for products administered to a patient more than once, the risk in terms of safety and reduced efficacy of switching back and forth between an interchangeable product and a reference product will have been evaluated. In practical terms, FDA requires that a sponsor submit additional data, most notably a clinical switching study, beyond that used to establish biosimilarity. This data and studies come at significant expense to the sponsor.

The designation is not reflective of therapeutic superiority to a biosimilar product. All biosimilar medicines are approved by FDA to have no clinically meaningful differences to the reference product. Manufacturers may choose to seek the designation but are not required to do so.[32]

The interchangeability designation allows a pharmacist to substitute an interchangeable product for the prescribed reference product in accordance with state law. U.S. patients are already accustomed to pharmacy substitution of small molecule drugs. When a patient goes to a pharmacy to pick up a prescription drug, a pharmacist may provide the patient with an equivalent and interchangeable generic medicine without having to consult the prescriber.

Each state has its own pharmacy practice laws that govern the practice of pharmacy regarding the use of brand-name and generic prescription drugs. Because biosimilars were not available when generic substitution laws were developed, states must continue to update their pharmacy practice laws to allow for substitution of interchangeable biologic products. Many states have already passed legislation reflecting this change.

The interchangeability designation is unique to the United States. In Europe, for example, no additional regulatory evaluation is required to indicate the interchangeability status of a biosimilar; the decision to allow for pharmacy substitution of a biosimilar is made by relevant national authorities. In the U.S., ensuring that manufacturers can obtain an interchangeability designation through an economically viable process will be an important part of manufacturers' ability to directly deliver lower-cost options to patients. Current draft guidance from FDA indicates that manufacturers will need to conduct complex and costly multi-switch clinical trials in U.S. patients to demonstrate interchangeability.[33] Providing regulatory clarity for manufacturers who wish to pursue interchangeability will directly affect the overall savings available through biosimilars.

EXTRAPOLATION

A biosimilar product may be approved for an indication of the reference product without direct studies of the biosimilar in that indication using a well-known scientific concept called "extrapolation." Biosimilar medicines are approved based on the totality of evidence presented in their applications, which rely on the use of data gathered during the development of the reference products and advanced analytical technologies to demonstrate biosimilarity. The extensive characterization of the reference product and analytical demonstration of biosimilarity between the products is typically reconfirmed with a clinical study in a single indication to affirm that the mechanism of action of biosimilar and reference product performs as expected. To that end, if the biosimilar manufacturer can demonstrate biosimilarity to the reference product it is possible for the biosimilar manufacturer to use data and information to scientifically support the approval for reference product indications that were not clinically studied by the biosimilar manufacturer. Extrapolation of indication is critical to improving access by reducing the cost of the biosimilar development and approval process.

Some advocates have called for FDA to limit the use of extrapolation,[34] suggesting that biosimilar manufacturers should be required to conduct additional clinical trials for each of the biosimilar's indications. This is contrary to the science behind biosimilarity and the intent of Congress in establishing the abbreviated regulatory pathway for biosimilars.[35] Forcing biosimilar manufactures to repeat research that has already been studied not only exponentially increases the cost and timeline for developing a biosimilar, but significantly reduces the incentive to pursue these products. Additionally, it has been noted that repeating clinical trials in patients, when these studies have already been completed with the reference product, is an unethical medical practice.[36]

Reimbursement and Market Access

Since the commercial introduction of the first FDA-approved biosimilar in 2015, FDA, along with the Centers for Medicare and Medicaid Services (CMS), Congress, state legislatures and other policymakers, have addressed many critical policy issues that affect the U.S. biosimilar market. None may be as important to the nascent market as ensuring a reliable reimbursement system. Like all medicines, biosimilars are part of a complex payment system involving providers, payors—including the federal government—supply chain entities and patients. Predictable reimbursement and market access is a key factor for manufacturers considering whether to invest in the pursuit of approvals and launches of these products. Without policies that ensure vibrant markets, it will be difficult for would-be biosimilar manufacturers to justify allocating significant capital into development programs without a reasonable potential for commercial success.

Changes to Medicare Part B

Because biologic medicines are often administered at various sites of care, there are multiple payment systems that biosimilar manufacturers will rely on to ensure that patients have access to their medicines, including the distinct systems set up by multiple federal payors. For the numerous products that are traditionally administered in physicians' offices or hospital settings, Medicare Part B plays an important role in driving provider adoption.

In late 2017, CMS revised its policy regarding reimbursement for biosimilars in Medicare Part B to establish a unique coding and reimbursement structure for biosimilars.[37] It puts biosimilars on a level playing field with their reference products and helps ensure the viability of the biosimilars market in outpatient settings by increasing manufacturer confidence in reliable reimbursement. A recent study also found that the revised policy would save the Medicare program $11.4 billion over 10 years by fostering biosimilar competition in the market.[38]

PASS-THROUGH STATUS FOR BIOSIMILARS

As federal agencies have been working to create new policies to incent biosimilar utilization, some policymakers have sought changes to outpatient reimbursement that would disadvantage biosimilar manufacturers when compared to their branded counterparts.

To encourage the use of innovative products and help ensure they would be available to Medicare patients, Congress in 1997 established pass-through "transitional" reimbursement payments for new medical devices, drugs and biologics in the Medicare Part B program.[39] These payments are designed to support the introduction of new medicines and provide manufacturers of new products an opportunity to familiarize prescribers with their products when they are first brought to market.

In its 2015 Hospital Outpatient Prospective Payment System (HOPPS) rule,[40] CMS began providing pass-through payments for biosimilars. These transitional payments are meant to encourage manufacturers to invest in biosimilar development as well as increase education for physicians and patients on the quality and safety of the biosimilar. The agency rationale was that because biosimilar manufacturers create their own

innovative processes for producing their biosimilar, they are not simply copying work already done by the reference product manufacturer.

Nonetheless, Congress recently considered a bill that would have prohibited biosimilars from receiving pass-through status. While this provision was ultimately removed from the final legislation, there is reason to be concerned that originator biologic manufacturers will continue to advocate to disadvantage their biosimilar competitors. The underlying goal of the pass-through program continues to be important to biosimilar manufacturers: to give providers reliable reimbursement in the first years after a product launches to allow for market adoption. This is provided to each new brand product on the market, and is equally important for biosimilars, which require extensive provider education when they are first launched.

Medicare Part D

For products that are dispensed in traditional retail pharmacies, Medicare Part D and traditional commercial insurers are important gatekeepers in ensuring that biosimilars receive the type of formulary placement that allows patients to realize the savings created by biosimilars. There have been two recent changes to the Medicare Part D program that will serve to sustain the development of the biosimilar market in the U.S.

The first involves leveling the playing field between biosimilars and biologics in the Medicare Part D coverage gap. Once in the coverage gap, patients have greater out-of-pocket exposure until their True Out-Of-Pocket (TrOOP) spend reaches the catastrophic stage threshold, where a patient has exposure to no more than 5 percent of costs.[41] To help alleviate patient distress while in the gap, Congress created the Coverage Gap Discount Program (CGDP), which requires manufacturers to provide discounts on their products to patients while they are in the coverage gap. That discount is also counted toward the calculation of TrOOP, along with beneficiary contributions, and helps patients bridge the gap to the catastrophic stage more quickly. Previously, biosimilar manufacturers were not eligible to pay these discounts, leaving patients and Part D plans to pick up the cost differential. Plans and patients could avoid this burden by choosing the brand reference product. To this end, Part D plans had little incentive to give biosimilars prominent formulary placement over more expensive brand reference products.

By creating a system that provides incentives for all members of the pharmaceutical supply chain to use lower-cost biosimilars, patients will be able to better realize the savings created by competition and biosimilar manufacturers will be able to rely on a sustainable market that rewards competition.

Congress recently amended the CGDP to allow biosimilar manufacturers to pay the discount previously paid only by their brand competitors. This places biosimilars on a level playing field to compete for placement on Part D plans' formularies, and will reduce beneficiaries' out-of-pocket costs as well as Part D program spending.[42]

Additionally, CMS recently lowered the biosimilars and interchangeable biologics copay for the Low-Income Subsidy (LIS) population to be equal to the copay of generic products. Previously, LIS patients taking a biosimilar were forced to pay the higher brand product copay for biosimilar products. This change will increase patient access and lower beneficiaries' out-of-pocket costs.[43]

These new policies represent the types of incentives necessary to foster a competitive biosimilars market, but are not in themselves sufficient to create a sustainable market. Additional systemic changes are needed to align incentives across the value chain.

Exclusionary Contracting Practices and the Rebate Trap

A significant obstacle to the development of a robust biosimilars market in the U.S. is anti-competitive market access tactics utilized by brand biologic manufacturers. Upon entry of a competitive biosimilar, some originator manufacturers have threatened to remove rebates they provide to payors unless the biosimilar is effectively excluded from the market. These contracts are a significant barrier.[44]

Examples of the "Rebate Trap"

		Post-Biosimilar	
	Pre-Biosimilar	50% of Patients Switch	100% of Patients Switch
Reference biologic list price, US $	50,000	50,000	50,000
Reference biologic postrebate price, US $	25,000	NA (no longer offering rebate)	NA (no longer offering rebate)
Biosimilar price, US $	NA	10,000	10,000
Patients taking branded biologic, No.	1,000	500	0
Patients taking biosimilar, No.	NA	500	1,000
Payer cost, US $	25,000,000	30,000,000	10,000,000

Source: Hakim A, Ross JS. Obstacles to the Adoption of Biosimilars for Chronic Diseases. JAMA. 2017;317(21):2163–2164. doi:10.1001/jama.2017.5202

Here is how it works: if a biosimilar manufacturer wishes to gain market share, it must enter the market at a significant discount from the reference product. However, if an insurer has contracted with a biologic manufacturer for a rebate on the reference product, even if that rebate is less than the discount the biosimilar offers, the plan must decide to either keep the biosimilar off its formulary or pay the full list price for the reference product, which would no longer offer rebates for its products if a biosimilar is allowed onto the formulary. In another variant, the manufacturer of the originator product will withdraw the rebates on a basket of products in the event that the contracted entity utilizes a biosimilar in place of the reference product. Both scenarios involve withdrawal of a rebate for the originator that was previously available. This is known as the "rebate trap", or "stacked rebates",[45] and acts as a significant disincentive to add a biosimilar to the formulary, without which it cannot gain market share.

The most high-profile example of this anti-competitive tactic to date is the subject of a lawsuit Pfizer filed against Johnson & Johnson (J&J). Pfizer has accused J&J of "exclusionary contracts" and price manipulation "to maintain its monopoly" for its reference product Remicade.® [46] This lawsuit stems from Pfizer's entrance to the market with its Remicade biosimilar, Inflectra, which Pfizer has reported is currently priced at a 17 percent discount to Remicade.[47]

While J&J claims that "Pfizer has failed to demonstrate sufficient value to patients, providers, payors and employers"[48] with its biosimilar, it is important to note that in J&J's motion to dismiss the lawsuit, the company did not dispute any of Pfizer's claims. Remicade reportedly earned $5.4 billion in revenue in 2017; Inflectra had 2017 revenue of $420 million.[49] If brand-name manufacturers can eliminate the financial viability of less-expensive biosimilars, there will be no potential for future investment, effectively ensuring long-term monopolies far beyond congressional intent. FDA Commissioner Gottlieb has recognized this threat, noting "Manufacturers are using several schemes to hamstring biosimilar competition…restrictive contracting, rebating, and distribution agreements deter coverage and reimbursement…the net result is a lopsided playing field that disincentives biosimilar developers from making the sizable investment in bringing such products to market. I am concerned this will lead to reduced competition in the long-run and unsustainable costs."[50]

The Patient Perspective

Building the Biosimilars Marketplace: Education and Combatting Misinformation

In addition to policies that foster a robust marketplace, prescriber and patient confidence is crucial to the adoption of these innovative medicines. The potential patient access and savings benefits resulting from biosimilars cannot be realized without significant buy-in from these key stakeholders. Education on the value, safety and efficacy of biosimilar medicines is an integral piece of the market development puzzle. A broad range of health care professionals will be engaged in biosimilars prescribing, dispensing and utilization. This includes doctors, physician assistants, nurses and pharmacists, and education tailored to each role is important. Similarly, collaboration with patient advocacy groups and disease-specific organizations to improve understanding is essential to acceptance of biosimilars. Absent provider and patient acceptance, affordability alone is unlikely to foster market adoption.

Unfortunately, misinformation threatens to slow biosimilar uptake and undermine confidence in these FDA-approved products. These efforts, often driven or silently funded by reference biologic manufacturers, are intended to sow doubt among patients and prescribers regarding biosimilars' safety and efficacy, and construct regulatory, policy and legal roadblocks to competition. This misinformation often takes advantage of the unfamiliarity stakeholders have with biologic medicines, including biosimilar medicines, and the important role they play in addressing serious or life-threatening conditions.

Such misinformation threatens the health of the patients who stand to benefit most from these treatments. It is important to focus on the facts about biosimilar medicines, including their safety, efficacy and lack of clinically meaningful differences from reference products. FDA has recently launched an education campaign[51] aimed at educating prescribers, and plans to release additional materials focused on patients in the future. Continued collaboration between FDA and other health care stakeholders will be critical to promote the facts about biosimilars, which is critical to ensure that patients benefit from biosimilar adoption.

Switching Reference Medicines

As more biosimilars enter the U.S. market, a frequent topic of discussion is whether switching patients who are stable on a reference medicine to a biosimilar may be dangerous, either as a result of immunogenicity or adverse reaction to a new medicine. A growing body of scientific data suggests otherwise. A recent systematic literature review found that switching to a biosimilar carried a low risk of safety issues or loss of efficacy and was not dangerous to patients.[52] The review comprised 90 biosimilar switching studies conducted on more than 14,000 individuals and involving seven molecular entities used to treat 17 disease indications. The review concludes, "Overall, the results suggest a low risk of either a safety concern or a loss of efficacy after switching to a biosimilar."[53]

One of the study's co-authors, Avalere Senior Vice President Gillian Woollett, M.A., DPhil, stated the study is aimed at reassuring all biosimilar stakeholders that, "even though no clinical differences are expected when patients are switched from a reference product to a biosimilar, indeed none are found. Hence, we confirm

the expectation already established through the application of sound regulatory science."[54] That confirmation can help all stakeholders feel comfortable with biosimilars. The conclusions of this large systematic review were corroborated by another, albeit smaller, review that included 53 biosimilar switching studies.[55]

In Europe, patients have used biosimilars for more than 10 years, resulting in more than 700 million patient days of safe, effective use.[56] The EU monitoring system for safety concerns has not identified any difference in the nature, severity or frequency of adverse effects between biosimilars and their reference medicine.[57]

Ultimately, patients' long-term health is paramount when deciding a treatment plan. In instances where the evidence has demonstrated that a lower-cost therapy offers the same outcomes for patient health, both providers and patients should have this information readily available to assist in their clinical decision-making. In such instances it may make sense that payors be given the opportunity to create financial incentives for the patient to use the lower-cost biosimilar, ultimately passing those savings on to the patient.

Conclusion

Biosimilars mean new access to life-saving medicines for millions of patients. They do so while also promising savings for patients and the U.S. health care system. FDA Commissioner Gottlieb recently highlighted the importance of fostering the development of a strong biosimilars market, saying: "The public health benefits of a robust, competitive market for biosimilars are impossible for us to ignore. Strong market incentives are critical to future biosimilar development in the same way these incentives are key for the development of innovator drugs and biologics."[58]

The promise of these innovative therapies can be realized only if policies are put into place that promote the development of a robust market:

- Addressing anti-competitive market access tactics by brand-name pharmaceutical firms
  - » Passing the CREATES Act to stop restricted distribution abuses
  - » Addressing the creation of "patent thickets" by brand pharmaceutical firms
  - » Maintaining the integrity and strength of the IPR process
  - » Passing the PACED Act to close the loophole sovereign immunity represents for protection of pharmaceutical IP patents
- Preventing the inclusion of provisions in trade agreements that would create barriers to market entry and delay or prevent timely biosimilar competition.
- Resolving regulatory uncertainty and market entry challenges
  - » Revising and/or finalizing FDA guidance on biosimilars naming, labeling and interchangeability
- Continuing development and implementation of policies that provide consistent and predictable reimbursement for biosimilar products
  - » Protecting pass-through status for biosimilars
  - » Confronting monopolistic contracting practices
  - » Aligning of incentives throughout value chain
- Continuing education of key constituencies regarding the quality, safety and effectiveness of biosimilars

Patients continue to reap the benefits of significant advances in specialty biological medicines with longer and healthier lives. However, the cost of these products continues on an unsustainable upward trajectory. By addressing the issues currently preventing robust biosimilar competition, policymakers can help ensure the development of a sustainable biosimilars market in the U.S. that will benefit patients through greater accessibility and lower prices.

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