MILLIMAN WHITE PAPER

The evolution of biosimilars in the United States

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Abstract

As the 10th anniversary of the first biosimilar approval in the United States approaches, understanding how the biosimilar environment has changed since 2015 will be key for providers, patients, payer organizations, and policymakers hoping to realize the benefits of biosimilars.

Introduction

Since the U.S. approval in 2015 of the first biosimilar, Zarxio (biosimilar to Neupogen), the potential for biosimilars to serve as analogs to generic drugs in the biopharmaceutical space has evolved. Gross prescription drug expenditures increased 16%, driven by a 25.1% increase in non-retail pharmacy expenditures (i.e., drugs administered in an inpatient setting).[1] Biosimilar competition with high-cost biological products—which are more common in non-retail pharmacy—can be a possible solution to reducing this trend in healthcare expenditures.

However, in the initial years following Zarxio's launch, several barriers—regulatory approval process and patent litigations, interchangeability status, provider reimbursement, and prescription drug rebates, among others—appeared to stall this momentum. In our 2018 analysis of the challenges facing biosimilars we concluded that, for biosimilars to achieve cost savings in the healthcare system, barriers must be reduced or eliminated.[2]

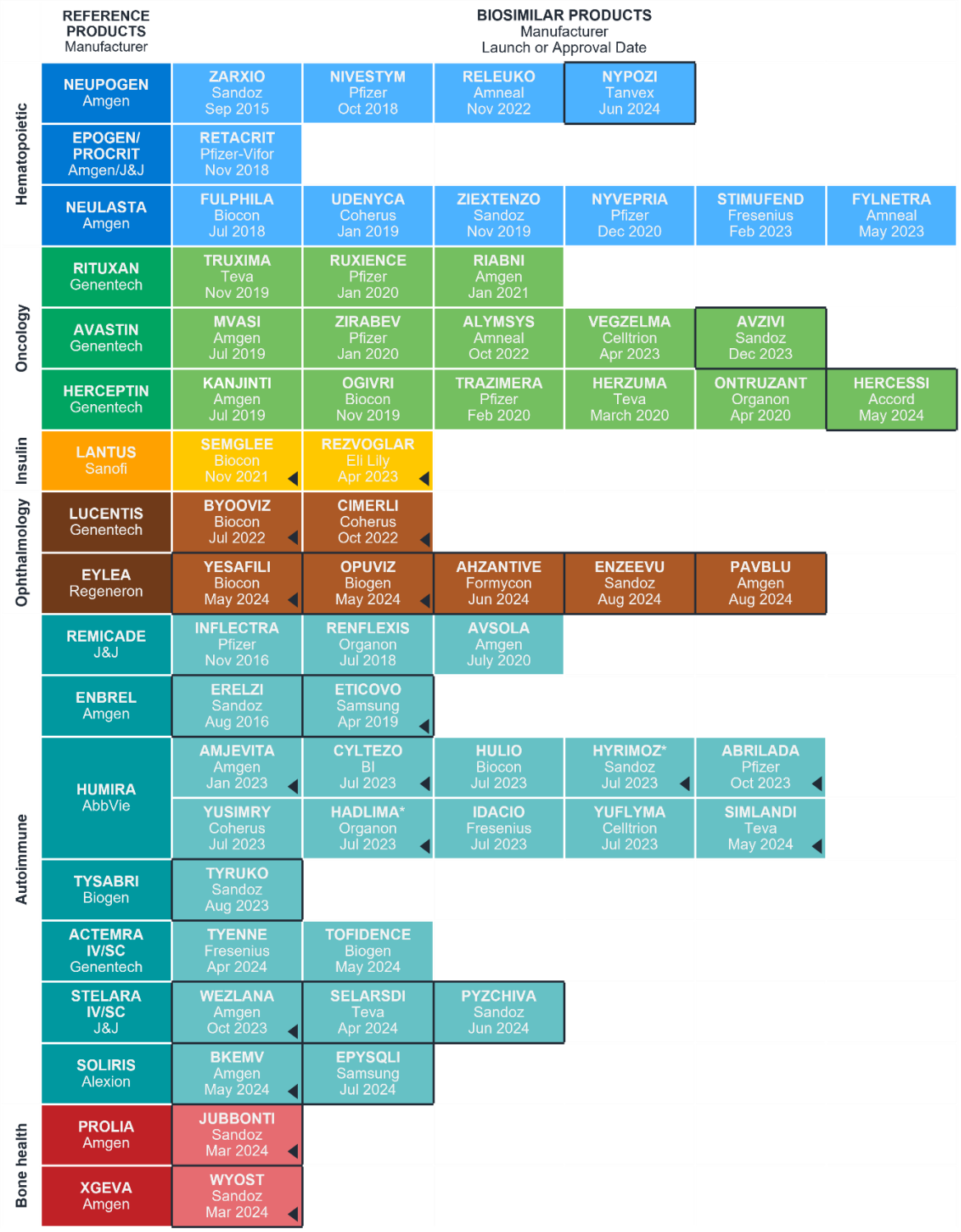
Notable progress has been made toward reducing these barriers and creating opportunities for biosimilar uptake. Providers are becoming increasingly receptive to biosimilars, with organizations such as the Mayo Clinic and Kaiser Permanente embracing concerted and holistic efforts to increase biosimilar utilization.[3,4] Perceptions of biosimilars as less efficacious or safe relative to the reference biologic, should lessen following the U.S. Food and Drug Administration (FDA) guidance in January 2024 that biosimilars no longer require labeling to indicate whether they are interchangeable. In addition, there was a recent decision in Europe to classify all approved biosimilars as interchangeable, with a recent scientific publication in the United States arriving at a similar conclusion.[5] Some reimbursement hurdles, such as the incentive for Medicare organizations to cover the higher-cost biologic reference product in exchange for higher rebates, may also diminish with provisions from the Inflation Reduction Act (IRA).

While there are still challenges for biosimilar adoption in the U.S. market, recent developments continue to emerge, such as the provisions from the IRA. These new pathways could evolve the biosimilar landscape and reduce biosimilar barriers, which can create more opportunities for biosimilar uptake and provide savings for the healthcare system.

Biosimilar landscape

Biologic drugs, complex molecules derived from living organisms, have become a growing piece of drug spending in the United States. In 2021, spending on biologics was about $260 billion, just under half of all drug spend.[6] While small-molecule drugs may have lower-cost generic versions that are chemically equivalent to the brand, biologics have biosimilar products that are highly similar to the reference biologic.[7] As of September 2024, there are currently 59 approved biosimilar products, though only 41 are currently in the market, as shown in Figure 1.[8]

FIGURE 1: U.S. BIOSIMILAR PRODUCT LANDSCAPE AS OF SEPTEMBER 2024



*Hyrimoz and Hadlima biosimilars are only interchangeable for certain dosages.

One source estimated that use of biosimilars instead of reference biologics saved $24 billion between 2015 and 2022, representing $9.4 billion in savings in 2022 alone. Biosimilars on average launch at list prices under 50% of the reference product, though some products offer only minimal cost savings.[9] Over 100 potential new biosimilars are being developed currently, and at least 10 additional reference biologics are expected to have biosimilar competition by 2027.[10,11] Notwithstanding the expansion of biosimilar options, potential savings from biosimilar competition have been limited by barriers.

Evolution of barriers to biosimilars

REGULATORY APPROVAL AND PATENT LITIGATIONS

One of the barriers to greater biosimilar acceptance in the United States has been regulatory approval. The FDA's approval of biosimilars is contingent on their efficacy and safety relative to the reference biologic. These metrics are evaluated by the FDA using several studies, including animal studies and clinical studies. Importantly, the application for approval must demonstrate the same clinical effectiveness as the reference product.[12]

Contrasting the experience of Europe and the United States indicates that greater regulatory scrutiny of biosimilars in the United States may have slowed the number of biosimilar approvals. Historically, European regulators were quicker in approvals of biosimilars, with Europe's first biosimilar approval in 2006 coming nearly a decade before the first in the United States. The difference in pace of regulatory approval between the two markets persisted throughout the 2010s, due in part to the slower development of a regulatory framework for biosimilar approval in the United States.[13] However, in the 2019-2021 period, the FDA approved more biosimilars than the European Medicines Agency (EMA), indicating that the United States is catching up to Europe.

Patent litigations have also delayed biosimilars from launching in the U.S. market. For example, the first Humira biosimilar, Amjevita, was approved in September 2016 but did not launch until nearly seven years later, in 2023, due to patent litigations. As of May 2023, nine of the 40 biosimilars approved at the time had launched without any patent disputes.[14]

INTERCHANGEABILITY

Of the 59 approved biosimilars, 17 have also been FDA-approved as "interchangeable biosimilars" as of September 2024.[11] Interchangeable status means a biosimilar can be substituted for the reference product by a pharmacist without requiring a new prescription from the physician, much like generics (this is also known as pharmacy-level substitution).[15]

The FDA issued guidance in January 2024 that biosimilars no longer require labeling to indicate whether they are interchangeable.[16] The FDA's rationale was that such labeling may have led to a perception among healthcare providers that a biosimilar not labeled as interchangeable was not as safe or effective as one that is. This decision is supported by an October 2023 published meta-analysis, which did not indicate a difference in the safety outcomes of biosimilars relative to reference products and is cited on the FDA website.[17,18]

For biosimilars without interchangeable status, provider hesitation to prescribe a biosimilar can be a barrier to market uptake. A survey of U.S. physicians currently prescribing biologics showed a majority are comfortable prescribing an interchangeable biosimilar and are similarly comfortable with pharmacy-level substitution. This survey highlights the importance of the interchangeability status of biosimilars and making unbiased safety and efficacy information about biosimilars available to prescribers.[19]

PROVIDER REIMBURSEMENT

Most biosimilars in the market today are physician-administered and covered under a medical benefit. The amount of reimbursement a physician receives for administering biologics and biosimilars differs by a patient's insurance coverage type.

Commercial payers typically reimburse drugs in the medical benefit based on a percentage of the amount billed by providers, known as the "buy-and-bill" method. This reimbursement method disincentivizes use of lower-cost biosimilars because a provider would lose profit with a lower-priced product. Reimbursement for brand drugs in a hospital setting is on average 247% of acquisition costs according to one Milliman study.[20] Alternative reimbursement strategies in the commercial market may incentivize provider prescribing of biosimilars. Milliman tested an alternative mechanism where payers would prospectively share savings from using lower-cost biosimilars between payers and providers. Savings were projected in this analysis, but the savings differed by site of service (physician office versus hospital outpatient department) due to the costs required to incentivize provider biosimilar use in the hospital outpatient setting.[21] Reimbursement for physician-administered drugs in Medicare Advantage typically follows the commercial market.

In Medicare fee-for-service (FFS), payments for drugs in the medical benefit are set at average sales price (ASP) plus 6%. Prior to the IRA, CMS reimbursed biosimilars at the biosimilar's ASP plus 6% of the reference product's ASP, as long as the biosimilar's ASP is less than the reference product's ASP. This approach effectively removed the financial incentive for a provider to choose a biosimilar and reference product, because the 6% add-on is the same dollar value for either. Due to the IRA, for five years beginning October 2022, biosimilar reimbursement increases to the biosimilar ASP plus 8% of the reference product's ASP.[22] Given this reimbursement method, Medicare FFS reimbursement results in a higher add-on payment for the biosimilar over the biologic which may drive increased adoption of biosimilars.

Figure 2 illustrates the reimbursement providers receive for administering biologics and biosimilars based on the patient's medical benefit coverage type. In this example we assume all providers purchase the drug at the July 2024 ASP.[23] When a patient has commercial coverage, we assume the provider is reimbursed 110% of acquisition costs in a professional office and 200% of acquisition costs in a hospital outpatient department.

FIGURE 2: ILLUSTRATIVE EXAMPLE OF PHYSICIAN AND HOSPITAL PROVIDER REIMBURSEMENT FOR REMICADE AND BIOSIMILAR RENFLEXIS

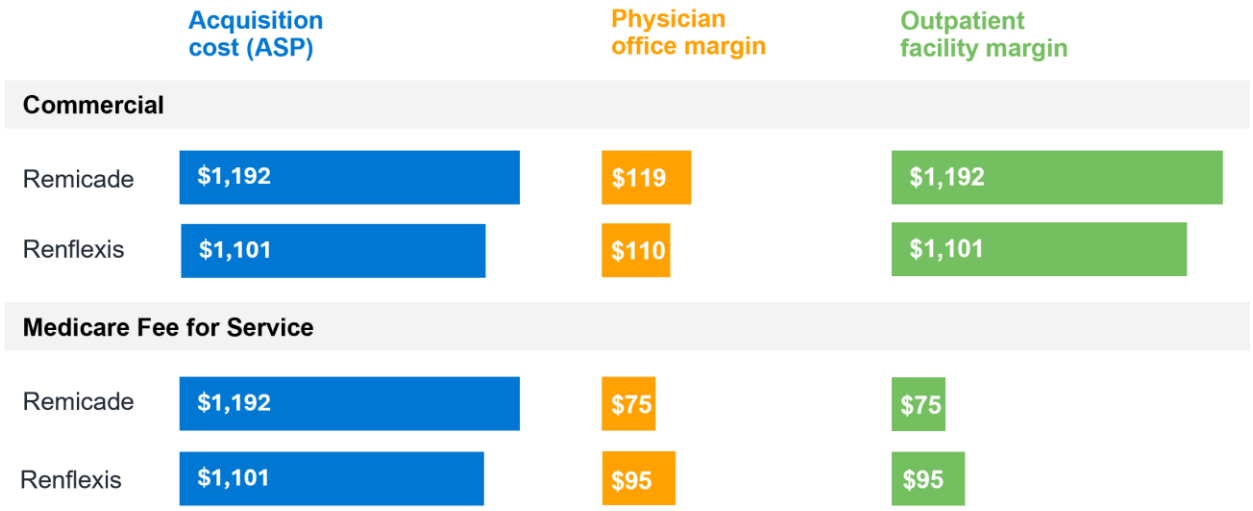


Figure 2 shows how a provider would receive higher reimbursement for the biosimilar over the biologic for Medicare patients, and in contrast would receive higher reimbursement for the biologic over the biosimilar when seeing patients with commercial coverage, especially in the outpatient setting.

PRESCRIPTION DRUG REBATES

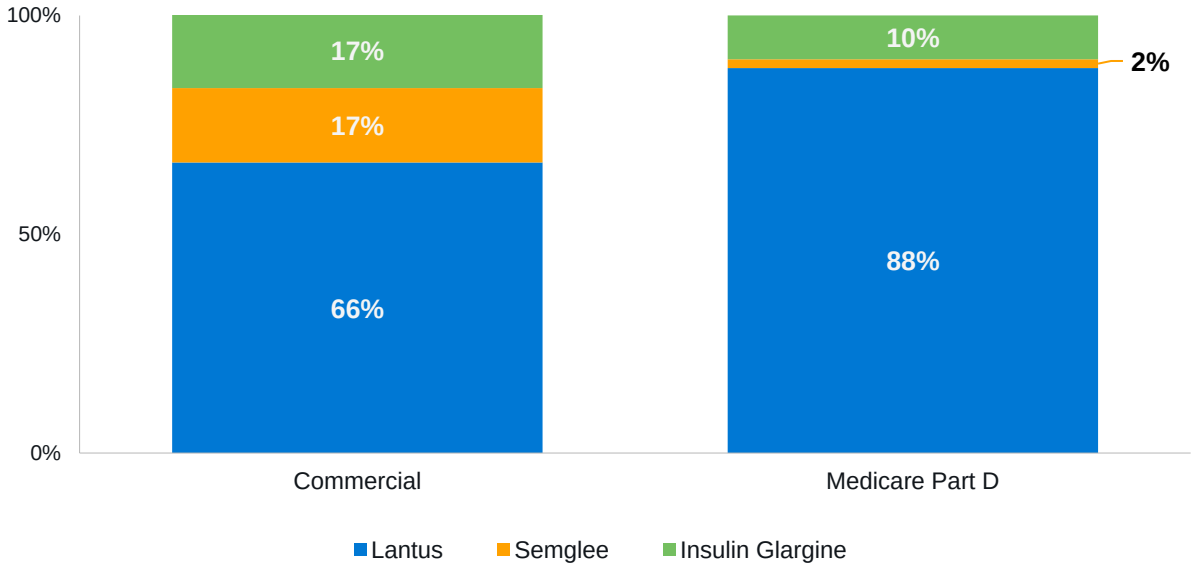
Manufacturers negotiate rebate agreements with pharmacy benefit managers (PBMs) to ensure that their brand drugs remain on the formulary or on a preferred formulary tier. Reference product manufacturers can compete by increasing their rebates to encourage a payer to exclude biosimilars from the formulary. In Medicare Part D, plans have financial incentives to favor higher-priced, higher-rebated reference products rather than lower-priced, lower-rebated biosimilars. While these financial incentives to favor high-priced drugs with high rebates may be somewhat reduced under the IRA, rebates remain important to plans' financials and competitiveness, influencing formulary coverage and the uptake of biosimilars.

Formulary coverage and uptake of biosimilars

The biosimilar launches for Lantus and Humira have brought the biosimilar discussion into the pharmacy benefit space where formularies are managed by PBMs and/or plans. As more biosimilars come to market in the pharmacy benefit, formulary coverage of biosimilars will be critical to increasing biosimilar market share. In every market—Medicare Part D, Medicaid, commercial—prescription drug rebates factor into formulary coverage and/or tier placement.

Lantus and its biosimilars—Semglee and insulin glargine—provide an example of increased biosimilar uptake due to reduced barriers in the commercial market. Both biosimilars are interchangeable, which should limit clinical-based provider and patient hesitation. As of July 2023, the 30-day wholesale acquisition cost (WAC) price for Lantus was $292 compared to $269 for Semglee and $99 for insulin glargine.[24] Figure 3 shows that Lantus biosimilars have made some inroads in the commercial market, with Semglee and insulin glargine each making up about one of every six prescriptions by the first quarter of 2023, or one of every three prescriptions combined. In contrast, in Medicare Part D, insulin glargine's market share was only 10% while Semglee had minimal market share (2%), which was likely related to competitive rebates offered in 2023.[25]

FIGURE 3: LANTUS AND BIOSIMILARS SEMGLEE AND INSULIN GLARGINE, COMMERCIAL AND PART D MARKET SHARE AS OF Q1 2023



A driving factor in the market share difference for Lantus and its biosimilars is formulary coverage. In 2023, none of the three largest PBMs, enrolling 65% of the commercial market, covered the unbranded insulin glargine.[26,27] One of the largest PBMs covered only Semglee, and the other two large PBMs also covered the reference product Lantus.[28,29,30] In Medicare Part D in 2023, Lantus was covered for about 85% of Medicare beneficiaries,[31] while only about 1% and 2% of members were enrolled in plans covering Semglee and insulin glargine, respectively. In 2024, formulary coverage changed for both the commercial and Medicare Part D market. Due to the insulin price reduction, one large PBM is now covering the new interchangeable biosimilar Rezvoglar along with Lantus on Tier 1, the lowest-

cost tier, for commercially insured members.[32] As of 2024 in the Medicare Part D market, Lantus is covered for only two-thirds of beneficiaries while Semglee is now covered for 9%; insulin glargine coverage remained at 2%.

Will similar uptake be seen for the new Humira biosimilars? Most manufacturers of Humira biosimilars have released both low-cost (about 80% off the Humira price) and high-cost (about 5% off) versions. In the commercial market, PBMs appear to include both low-cost and high-cost versions of the Humira biosimilar on their formularies.[33] One of the large PBMs removed Humira from its formularies starting in April 2024.[34]

In 2024, for Medicare Part D, Humira continues to be covered (on the specialty tier) for almost all members. Of the Part D enrollees who have access to a Humira biosimilar, half of these enrollees are in plans that have access to only one Humira biosimilar, while the other half have access to at least two Humira biosimilars. Cyltezo (high-cost and interchangeable biosimilar) is covered for about 60% of Part D enrollees and Hyrimoz (low-cost biosimilar) is covered for about 30% of Part D enrollees, where the other Humira biosimilars have minimal coverage (less than 5% of enrollees). When a biosimilar product is on a plan's formulary, most plans place the biosimilar product on the same cost-sharing tier (typically the specialty tier) as Humira.[35]

The three largest PBMs have also now launched subsidiaries to distribute or produce biosimilars, which may continue to impact formulary decisions and access to biosimilars.[36]

How may the Inflation Reduction Act impact biosimilars?

The IRA has introduced many provisions that may impact the uptake of biosimilars in the Medicare Advantage (MA), Part B and/or Part D markets. Most provisions promote biosimilar utilization while others may inadvertently have a negative impact on biosimilar utilization, as shown in Figure 4.

FIGURE 4: INFLATION REDUCTION ACT PROVISIONS AND POTENTIAL IMPACT ON BIOSIMILAR UPTAKE

IRA Provision	Effective Date	Biosimilar impact	Potential impact on MA biosimilar uptake
Temporary biosimilar Part B 2% add-on payment	October 1, 2022	▪ Encourage providers to use biosimilars over reference biologics with higher reimbursement rates	
Inflation rebates	Part D: October 1, 2022 Part B: January 1, 2023	▪ Biosimilar uptake may vary by Part B vs Part D since penalties are based on net Average Sales Price (ASP) for Part B and gross Average Manufacturer Price (AMP) for Part D ▪ Some manufacturers will absorb the Medicare inflation penalty as higher prices/sales on other lines of business, like commercial, can offset these penalties so biosimilar uptake may remain status quo	
2025 Part D benefit redesign	January 1, 2025	▪ Plans focus on managing catastrophic spending which encourages promotion of less expensive biosimilars over reference products	
Price negotiation – maximum fair price	Part D: January 1, 2026 Part B: January 1, 2028	▪ Decreases the price difference between biologics and biosimilars, diminishing the value of biosimilars as the more cost-effective option ▪ Diminishing return on investment for biosimilar manufacturers could potentially deter or completely prevent product launches ▪ The negotiated MFP with CMS could be set at a price that discourages a biosimilar from entering the market	
Price negotiation – "Special Rule to Delay Selection and Negotiation for Biosimilar Entry"	Part D: January 1, 2026 Part B: January 1, 2028	▪ Changes in biologics manufacturer patents and launch strategies that may result in biosimilars coming to the market sooner to avoid price negotiation	

TEMPORARY PART B ADD-ON PAYMENT

As discussed above, section 11403 of the IRA implemented a temporary 2% increase in biosimilar reimbursement for a five-year period from October 1, 2022, through December 2027 for qualifying biosimilars (where the ASP of the biosimilar is less than the reference biologic).[37] Therefore, biosimilars will be paid at 108% of the ASP of the reference product (previously this was 106%). The add-on payment is intended to increase access to biosimilars, foster competition, and potentially decrease prices because of increased competition.[38]

INFLATION REBATES

The IRA included a Medicare inflation rebate where manufacturers are required to pay rebates to Medicare if their drug price increases are higher than the rate of inflation for Part B and D drugs, including biosimilars. Based on a Kaiser study, about half of Part B and D drugs covered by Medicare had price increases that exceeded inflation between 2019 and 2020.[39] The inflation penalties are based on ASP (net price) for Part B drugs and average manufacturer price (AMP) for Part D drugs. AMP does not include reductions in price from manufacturer rebates like ASP does. Given this difference, manufacturer pricing strategies could differ between Part B and D drugs to avoid inflation penalties, which may have different impacts on biosimilar uptake between Part B and D drugs. In addition, if manufacturers have little Medicare sales, then the Medicare inflation penalty will be immaterial. Therefore, some manufacturers may continue to increase prices above inflation as sales from other lines of business, like commercial, will more than offset the inflation penalties on the Medicare business. Also, inflation rebates are not applicable for Part B or D drugs that are eligible for 340B pricing.[40] IQVIA data estimated about 40% of Part D drugs are 340B-eligible.[41] Consequently, biosimilar uptake may remain status quo when accounting for other lines of business sales impact and 340B-eligible drugs not being subject to the inflation penalties.

2025 PART D BENEFIT REDESIGN

Under the IRA's Part D benefit redesign, Part D plan liability in the catastrophic phase will increase from 20% in 2024 to 60% in 2025. This redesign will significantly increase Part D plans' risk, which may incentivize plans to look for ways to manage the costs of members that use more expensive drugs through reassessment of their formulary and utilization management (UM) practices. One way to reduce costs for plans is to focus on lower-cost options such as biosimilars when developing formularies.

PRICE NEGOTIATION

Price negotiation implemented by the IRA allows the U.S. Department of Health and Human Services (HHS) to negotiate drug prices for selected Part D and Part B drugs beginning in 2026 and 2028, respectively. This negotiated drug price is also known as the maximum fair price (MFP). The IRA establishes the selection criteria and specifies how the timing of a biosimilar's launch affects whether the MFP stays in effect and whether the selected drug remains on the drug list. The following implications are based on when the biosimilar is available in the market for the 2026 selected Part D drugs:[42]

- **Biosimilar launched prior to August 1, 2024**: MFP would not be applicable in 2026 although the biologic remains on the selected drug list. Note that no biosimilars were marketed for the 2026 negotiated drugs so the MFP will be in effect in 2026 for the 10 Part D selected drugs.
- **Biosimilar launched between August 1, 2024**, and March 31, 2026: The biologic MFP would remain in effect for 2026, but cease to apply in 2027.
- **Biosimilar launched after March 31, 2026**: The biologic MFP would remain in effect for both 2026 and 2027 but the drug would be removed from the 2028 drug list.

Stelara, one of the selected Part D drugs for 2026, has a biosimilar, Wezlana, that was approved by the FDA on October 31, 2023.[43] However, the launch of Wezlana has been delayed to 2025 due to patent lawsuits, and therefore, the Stelara MFP will be applicable in 2026. It is possible Stelara's MFP would not apply in 2027 if its biosimilar is not further delayed beyond March 31, 2026. With a lower MFP, price negotiation will reduce incentives for biosimilar competition as the biologic and biosimilar price differential will be reduced in Medicare. Also, pipeline

biosimilar development and launches may be deterred as the market share potential is lower than expected, thus diminishing the return on investment.[44] This could lead to fewer biosimilar launches and alternatives to the selected drug.[45] In addition, the negotiated MFP with CMS could be set at a price that discourages a biosimilar from entering the market, such as a price lower than the potential biosimilar price—which reduces competition.

Additionally, under the IRA's "Special Rule to Delay Selection and Negotiation for Biosimilar Entry," biosimilar manufacturers can request to delay selection and negotiation of the corresponding reference product if they can prove their biosimilar will likely be launched within two years. Given this rule, some may anticipate changes in biologic manufacturer patent litigation and launch strategies that allow biosimilars to come to the market sooner so the biologic can avoid price negotiation.

Conclusion

While challenges persist, there have been significant strides toward greater biosimilar acceptance and utilization since the first U.S. biosimilar approval in 2015. On the regulatory side, the FDA appears to be aligning with the EMA's outlook on the safety of biosimilars with regard to interchangeability. In addition, the IRA provisions should increase the uptake of biosimilars in the Medicare market, which may spill over into other markets.

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