Will Interchangeable Biosimilars Do to Biologics What Generic Drugs Did to Brand Name Medications? Biosimilars and Cost Saving

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New, protein-based medications called *biologics* have begun to offer patients safe, highly effective medications for challenging conditions, including coronavirus disease 2019 (COVID-19) (1). But this promise comes with a downside; the Office of Inspector General (OIG) of the U.S. Department of Health and Human Services has noted that biologics are some of the most expensive medications on the market (2), and many people face barriers to these newer medications' therapeutic promises. Arguably, issues of access may be especially acute in the United States, where a unique regulatory environment and health system could be hindering the broader use of biologics. At the same time, various initiatives aim to address these access and cost concerns. In this brief, we discuss the introduction of interchangeable biosimilars (IBs), as well as efforts to encourage their use, particularly in the Medicare program.

Key points

- Biologics, such as insulin and novel protein-based medications, have therapeutic advantages over conventional drugs but are among the highest cost medications on the market.
- Through a new regulatory pathway, a "generic" version of biological drugs, known as interchangeable biosimilars (IBs), are now coming to market.
- The Inflation Reduction Act (IRA) (2022) aims to lower the price of biologics primarily by promoting biosimilars.
- Additional approaches to advancing biosimilar use and improving access are being tested, both in payment structures and regulation, as more IBs are set to become available.

Biosimilars: A "Generic" Alternative

Many biologics are under patent protection and are sold only under their brand name as originator products. In 2015, the Food and Drug Administration (FDA) licensed the first "biosimilar" medication. A biosimilar, as defined by the Biologics Price Competition and Innovation Act (2009), is a biologic medication that is clinically identical to an originator biologic drug (3, 4).

Of the 39 biosimilars currently approved by the FDA, three (insulin glargine-yfgn [Semglee®], adalimumab-adbm [Cyltezo®], and ranibizumab-eqrn [Cimerli®]) have been approved as IBs (5). This means that, depending on state regulations, pharmacists can substitute or switch IBs for a brand name product (6). The Biologics Price Competition and Innovation Act (2009) defined

parameters for achieving IB status. The biologic product must meet the biosimilar requirements, meaning it is highly similar with no clinically meaningful differences from the reference biologic. And, in order for the biosimilar to be an IB, it must also produce the same clinical result as the reference product in any given patient and be able to be switched back and forth from the IB to the reference product (7).

Insulin glargine-yfgn is the first IB available in the United States; it is interchangeable for the brand drug Lantus®, a long-acting insulin (6). The use of insulin as a therapy for diabetes was discovered approximately 100 years ago, producing remarkable and lifesaving effects in patients, even at the outset. Long-acting insulins, a later development, further stabilize blood glucose and have become the standard of care for diabetes. However, access to insulin continues to be limited by high costs (8). Approximately 25% of patients with diabetes who use insulin have reported not taking the medication as prescribed because of its cost (9). Patients who skip or ration their insulin are at risk for poor blood glucose control (9). The availability of insulin glargine-yfgn, the IB version of insulin glargine (Lantus®), may improve access to insulin, given evidence of similar effectiveness and safety (non-inferiority) from randomized controlled trials and lower list prices (10). However, the uptake of biosimilars in the United States may have been slowed by manufacturers of biologic originator products, and it is not yet clear that interchangeable biosimilars will result in increased competition and lower costs without further regulatory actions.

What is a Biosimilar?

A biosimilar is a biological product that is highly similar to, and has no clinically meaningful differences from an existing FDA-approved reference product.

What is an Interchangeable?

An interchangeable product is a biological product that meets all the requirements for a biosimilar product, but also meets additional requirements outlined by the Biologics Price Competition and Innovation Act (2009).

Adalimumab-adbm (Cyltezo®), the first IB for the brand name Humira®, the blockbuster drug for treating rheumatoid arthritis, will reach the U.S. market in 2023 (11). The latest IB, ranibizumab-eqrn (Cimerli®), interchangeable with Lucentis® is expected to be available in the market in October 2022. Over the next 5 years, the number of IBs is likely to expand 4-fold (12). IBs hold the promise of reducing health care spending by offering lower cost alternatives to high-priced biologic drugs (9).

Addressing Cost and Access Issues in Medicare Part D

In March 2022, a report from the OIG noted the potential for biosimilars to reduce costs for Medicare, especially as biologic medications become more common (2). The OIG noted that although biologics were used by less than 2% of the population, they cost Medicare Part D and its beneficiaries approximately $12 billion in 2019, with the likelihood of these costs growing as new biologics come on the market for chronic conditions that are prevalent in the Medicare population (2).

Both Part B and Part D expenditures on biologics are expected to rise because many biologics treat diseases prevalent in older adults, and the population of older adults is expected to increase rapidly as baby boomers age (2). The OIG issued two recommendations:

1. Medicare should encourage Part D plan sponsors to increase access and use of biosimilars.
2. Medicare should monitor biosimilar coverage on the formularies that Part D plan sponsors use to manage drug utilization.

Medicare concurred with the first recommendation and responded to the second recommendation with neither concurrence nor non-concurrence (2).

Formularies are a list of prescription drugs covered by a prescription drug plan or another insurance plan offering prescription drug benefits. Formularies have emerged as an essential tool used by payers to reduce medication costs, and monitoring ensures that formularies maintain medications patients need. Therefore, monitoring formularies as the OIG suggests may help ensure biosimilars are made accessible to Medicare beneficiaries. Monitoring would help address two challenges:

1. Formulary design focused only on cost; and
2. Rebates in exchange for preferred placement

The March 2022 report of the Medicare Payment Advisory Commission (MedPAC) offers additional data that reference product manufacturers may be using rebates or other incentives to payers to limit competition and how the Part D payment structure may contribute to these pricing strategies that depress biosimilar uptake (13). MedPAC notes that prior to insulin glargine-yfgn's approval as an interchangeable biosimilar, two other insulin follow-on products were approved by the FDA via the New Drug Application pathway rather than through the Biologics Price Competition and Innovation Act (2007). These products were launched in 2016 and 2018, but neither has achieved widespread adoption in Medicare Part D, with the reference product continuing to have the greatest market share (13). However, MedPAC compares Part D utilization data with data from Medicaid and finds that in Medicaid, these follow-on products have achieved substantially greater market share, perhaps due to the different payment

structures for Medicaid versus Medicare Part D. In many Medicaid programs, state payments to Medicaid payers are fully capitated, whereas Part D reimbursements are set according to cost-based reinsurance (13). In addition, most states have classified biosimilars in such a way that rebates from reference product manufacturers cannot lower the price below those of biosimilars for Medicaid (13). But in Part D, formularies may be incentivized to prefer medications with higher list prices and high rebates over medications with low list prices (13). Such a preference could be exploited to tamp down the competition and keep overall prices higher.

Compared to the insulin follow-on products MedPAC reviews, insulin glargine-yfgn is unique, as the first biosimilar with an interchangeable designation. Its average wholesale price for a pen injector (100 units/mL) is $11.84, compared to $34.02 for the brand Lantus Solostar® (14). Medicare beneficiaries not receiving the Low-Income Subsidy paid $54 per insulin prescription in 2020, so the cost savings associated with the IB of insulin glargine may be significant (15). The Inflation Reduction Act (IRA) (2022) caps monthly insulin costs to $35 for Medicare beneficiaries (15). That cap may indirectly encourage further adoption of insulin glargine-yfgn in plan formularies over insulin formulations that have a cost above the cap. Thus, interchangeable biologics (e.g., insulin glargine-yfgn) represent a new frontier in biosimilars and an opportunity to observe whether costs can be lowered for this class of medications that account for disproportionately high spending.

Reducing Costs for Biosimilars Administered in Doctors' Offices or Outpatient Hospital Settings

Although most medications are covered under Medicare Part D, medications administered by injection or infusion in physicians' offices or hospital outpatient settings are covered under Medicare Part B. Since 2009, medication costs related to this Part B have driven progressive increases in costs, rising to $40.7 billion in 2020, growing 10% per year from 2009 to 2019 (16). MedPAC's June 2022 report proposes policy changes to reduce drug costs in Medicare Part B, including a recommendation to change Medicare's reimbursement structure for drugs dispensed in outpatient settings (16). Current rules reimburse providers with a 6% add-on to the average sales price, which means that higher prices will result in higher reimbursement (6% of a higher cost drug will be worth more than 6% of a lower cost drug) (16,17). The Inflation Reduction Act (2022) has changed this rule so that now an 8% add-on will be applied to biosimilars in the hopes that this higher rate will remove the financial incentive for administering higher priced originator products (18). The OIG has also announced an inquiry into biosimilars in Medicare Part B, to be conducted in 2023 (19).

Innovative Approaches to Promote Biosimilars

Medicare has broadly acknowledged the need for implementing policies that will expand biosimilar use, and a renewed focus at the Centers for Medicare & Medicaid Services (CMS) on health equity suggests that increasing access to biologics for more patients will be a long-term priority (20, 21). In a February 2022 address, the CMMI chief strategy officer cited the efforts of researchers and policy analysts in overcoming such barriers, along with the CMMI's recommitment to testing models directed at greater health equity (22). Existing Medicare models may also identify methods to increase biosimilar adoption through value-based care initiatives. CMMI has been testing methods to align financial incentives with care coordination, appropriateness of care, and access for patients with cancer diagnoses through partnerships with providers and payers (23).

Additionally, the CMMI -Value Based Insurance Design (VBID) model may generate data on best practices for spurring biosimilar adoption. This model has a broad-reaching mandate for Medicare Advantage plans to test approaches for reducing program expenditures while enhancing care coordination and person- or disease-specific interventions (24). Among the interventions tested in 2023 are reductions in cost sharing for Part D medications and use of high-value providers in care management and disease-state management programs (24). Potentially, some participants may include biosimilars in their Part D cost-saving approaches. Whether VBID model participants can leverage IBs to achieve program goals with VBID flexibilities may help drive future Medicare Advantage changes.

Additionally, the Part D Senior Savings Model is comprised of plan sponsors who offer copays of no more than $35 for a month supply of a variety of insulins (25). These copays remain at $35 or lower throughout all phases of Part D coverage, deductible, initial coverage and coverage gap phases (25). This pricing is achieved by voluntary participation of five pharmaceutical manufacturers who agree to a 70% discount in the coverage gap, with those discounts calculated before Medicare's supplemental benefits are applied (25).

How the IRA May Affect Pricing of Biosimilars

The IRA includes provisions meant to lower drug prices for both Medicare and consumers and has been hailed as the achievement of policy goals that had floundered for decades (26, 27). The law's approach toward biologic pricing is largely consistent with the overall strategy behind the OIG report and MedPAC recommendations: to promote biosimilar adoption as a means of lower pricing through market competition.

The best-known drug pricing–related provision of the law is that Medicare will now be empowered to negotiate lower drug prices (27). Although this provision includes biologics as

medications eligible to undergo the negotiation process, its rules are written to promote biosimilars (26). Biologics will be eligible for price negotiation 13 years after initial approval and only if a biosimilar is not likely to be both licensed and marketed within 2 years of this eligibility timeline (26, 28). The wording of the law reflects a lesson learned on the licensing but delayed marketing of biosimilars for Humira® (26). Thus, although an originator biologic may enter the negotiation process, the entry on the market of an approved biosimilar will exempt that drug from price negotiations. This rule should promote additional marketing of biosimilars.

The impact of the IRA on insulin and Part B biosimilars has been previously noted, and the law may also affect the pricing of biologics through rebates to Medicare for drugs with prices that rise higher than the rate of inflation and in out-of-pocket spending caps. As the law is implemented and the biosimilar market continues to develop, it is believed that consumers will have lower cost options for these cutting-edge therapeutics (27).

Conclusion

Regulatory barriers to biosimilar access may begin to ease as Medicare prioritizes biosimilars as a way to increase access to effective medications at lower prices and as reimbursement rules and business practices that could be used to discourage biosimilar adoption come under investigation. These steps may well be crucial for achieving wider biosimilar use and lower cost biologics, but more IBs will need to be approved by the FDA. This summer, both the House of Representatives and Senate have advanced bills to continue the FDA user fee programs in which pharmaceutical industry applicants fund FDA reviews (29). These fees have become essential for FDA operations and cover biosimilar reviews.

Many older Americans continue to report not taking prescribed medications due to high cost (30). Medication nonadherence is thought to result in treatment failure, hospitalizations, and $528.4 billion in avoidable health system costs in 2016 (31). The cost of medications is likely to continue to rise, partly due to increased utilization of complex new medications, such as biologics. Will biosimilars result in lower medication prices as conventional generic drugs did? With IBs such as insulin glargine-yfgn and a major new law affecting drug pricing, a new answer to this question may be emerging.

List of FDA-Approved Biosimilars as of 10/27/2022 (5)

Reference product	Biosimilar name	Date of FDA approval	Approved indications	Biosimilars expected to enter into price negotiation based on IRA
Avastin® (bevacizumab)	Mvasi® (bevacizumab-awwb)	9/14/2017	• Cervical cancer, persistent/recurrent/metastatic • Colorectal cancer, metastatic • Glioblastoma, recurrent • Hepatocellular carcinoma, unresectable or metastatic • Non-small cell lung cancer, non-squamous • Ovarian (epithelial), fallopian tube, or primary peritoneal cancer • Renal cell carcinoma, metastatic	9/2028
	Zirabev™ (bevacizumab-bvzr)	6/27/2019	Same as above	6/2030
	Alymsys® (bevacizumab-maly)	4/14/2022	Same as above	4/2033
	Vegzelma® (bevacizumab-adcd)	9/27/2022	Same as above	9/2033
Enbrel® (etanercept)	Erelzi® (etanercept-szzs)	8/31/2016	• Ankylosing spondylitis • Plaque psoriasis • Polyarticular juvenile idiopathic arthritis • Psoriatic arthritis • Rheumatoid arthritis	8/2027
	Eticovo™ (etanercept-ykro)	4/25/2019	Same as above	4/2030

Reference product	Biosimilar name	Date of FDA approval	Approved indications	Biosimilars expected to enter into price negotiation based on IRA
Herceptin® (trastuzumab)	Herzuma® (trastuzumab-pkrb)	12/14/2018	• Breast cancer, adjuvant treatment • Breast cancer, metastatic • Gastric cancer, metastatic	12/2029
	Kanjinti® (trastuzumab-anns)	6/13/2019	Same as above	6/2030
	Ogivri® (trastuzumab-dkst)	12/3/2017	Same as above	12/2028
	Ontruzant® (trastuzumab-dttb)	1/18/2019	Same as above	1/2030
	Trazimera™ (trastuzumab-qyyp)	3/11/2019	Same as above	3/2030
Humira® (adalimumab)	Abrilada™ (adalimumab-afzb)	11/18/2019	• Crohn disease, moderate to severe, induction and maintenance of remission • Hidradenitis suppurativa, moderate to severe, refractory (Humira® only) • Juvenile idiopathic arthritis • Plaque psoriasis, moderate to severe • Rheumatoid arthritis • Spondylarthritis (both axial spondylarthritis and peripheral spondylarthritis) • Ulcerative colitis, moderate to severe, induction and maintenance of remission • Uveitis, noninfectious	11/2030
	Amjevita™ (adalimumab-atto)	9/23/2016	Same as above	9/2027
	Cyltezo® (adalimumab-adbm)[a]	8/29/2017	Same as above	8/2028

Reference product	Biosimilar name	Date of FDA approval	Approved indications	Biosimilars expected to enter into price negotiation based on IRA
	Hadlima® (adalimumab-bwwd)	7/22/2019	Same as above	7/2030
	Hulio® (adalimumab-fkjp)	7/6/2020	Same as above	7/2031
	Hyrimoz® (adalimumab-adaz)	10/31/2018	Same as above	10/2029
	Yusimry™ (adalimumab-aqvh)	12/20/2021	Same as above	12/2032
Lantus® (insulin glargine)	Rezvoglar™ (insulin glargine-aglr)	12/17/2021	• Diabetes mellitus, types 1 and 2	12/2032
	Semglee® (insulin glargine-yfgn[a]	7/28/2021	Same as above	7/2032
Lucentis® (ranibizumab)	Byooviz™ (ranibizumab-nuna)	9/20/2021	• Macular degeneration • Macular edema • Myopic choroidal neovascularization • Diabetic macular edema (Lucentis® only) • Diabetic retinopathy (Lucentis® only)	9/2032
	Cimerli™ (ranibizumab-eqrn)[a]	8/2/2022	Same as above	8/2033

Reference product	Biosimilar name	Date of FDA approval	Approved indications	Biosimilars expected to enter into price negotiation based on IRA
Neulasta® (pegfilgrastim)	Fulphila® (pegfilgrastim-jmdb)	6/4/2018	• Prevention of chemotherapy-induced neutropenia • Hematopoietic radiation injury syndrome, acute (Neulasta® only)	6/2029
	Udenyca® (pegfilgrastim-cbqv)	11/2/2018	Same as above	11/2029
	Ziextenzo® (pegfilgrastim-bmez)	11/5/2019	Same as above	11/2030
	Nyvepria™ (pegfilgrastim-apgf)	6/11/2020	Same as above	6/2031
	Fylnetra® (pegfilgrastim-pbbk)	5/27/2022	Same as above	5/2033
	Stimufend® (pegfilgrastim-fpgk)	9/1/2022	Same as above	9/2023
Neupogen® (filgrastim)	Nivestym® (filgrastim-aafi)	7/20/2018	• Chemotherapy-induced myelosuppression in non-myeloid malignancies • Acute myeloid leukemia following induction or consolidation chemotherapy • Bone marrow transplantation • Hematopoietic radiation injury syndrome, acute • Peripheral blood progenitor cell collection and therapy • Severe chronic neutropenia	7/2029
	Releuko® (filgrastim-ayow)	3/1/2022	Same as above	3/2033
	Zarxio® (filgrastim-sndz)	3/6/2015	Same as above	3/2026

Reference product	Biosimilar name	Date of FDA approval	Approved indications	Biosimilars expected to enter into price negotiation based on IRA
Procrit® (epoetin alfa)	Retacrit® (epoetin alfa-epbx)	5/15/2018	• Anemia due to chemotherapy in patients with cancer • Anemia due to chronic kidney disease • Anemia due to zidovudine in HIV-infected patients • Reduction of allogeneic RBC transfusion in patients undergoing elective, noncardiac, nonvascular surgery	5/2029
Remicade® (infliximab)	Avsola® (infliximab-axxq)	12/6/2019	• Ankylosing spondylitis • Crohn disease • Plaque psoriasis • Psoriatic arthritis • Rheumatoid arthritis • Ulcerative colitis	12/2030
	Inflectra® (infliximab-dyyb)	4/5/2016	Same as above	4/2027
	Ixifi™ (infliximab-qbtx)	12/14/2017	Same as above	12/2028
	Renflexis® (infliximab-abda)	4/21/2017	Same as above	4/2028
Rituxan® (rituximab)	Riabni® (rituximab-arrx)	12/17/2020	• Chronic lymphocytic leukemia • Granulomatosis with polyangiitis • Microscopic polyangiitis • Non-Hodgkin lymphomas	12/2031
	Ruxience® (rituximab-pvvr)	7/23/2019	Same as above	7/2030
	Truxima® (rituximab-abbs)	11/28/2018	Same as above	11/2029

Note. HIV = human immunodeficiency virus; IRA = Inflation Reduction Act; RBC = red blood cell.
[a] Interchangeable biologics; https://purplebooksearch.fda.gov/advanced-search

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