November 29, 2023

ISSUE BRIEF | Center for a Healthy America

Federal Barriers Make Biologic Drugs Unaffordable

Charlie Katebi

TOPLINE POINTS

- ★ Over the past 10 years, the cost of important prescription drugs known as biologics has skyrocketed.
- ★ A major reason brand-name biologics are so expensive is that they face little competition from generic versions known as biosimilar drugs. The Food and Drug Administration (FDA) imposes an expensive and burdensome approval process on biosimilars that blocks new ones from entering the market and competing with brand-name biologics.
- ★ Policymakers should introduce more competition and make biologics more affordable by reforming the FDA's approval process for biosimilar drugs.

Background

Since the 1860s, scientists and physicians have developed most medicines by synthesizing relatively simple chemical ingredients. Examples of these simple drugs, known as small-molecule drugs, include aspirin, penicillin, Ibuprofen, and antihistamines. Today, 90 percent of all medicines approved in the United States are small-molecule drugs (Coherent Market Insights, 2022).

Starting in the 1970s, scientists began to develop more complex drugs, known as biologics (Lybecker, 2020). Biologics are produced from components of living organisms, including human, plant, and animal cells, and microorganisms such as bacteria or yeast. Examples of biologics include Humira, Remicade, Herceptin, and Avastin. These biologics treat a range of diseases, including cancer, psoriasis, rheumatoid arthritis, and Crohn's disease.

Biologics are Unaffordable

During the past 10 years, the cost of biologics has increased dramatically. Between 2013 and 2021, patient and taxpayer spending on biologics increased from $100 billion

(IQVIA, 2018) to $260 billion (adjusted for inflation), a 160 percent increase (IQVIA, 2023). By 2018, biologic drugs accounted for only 0.4 percent of all prescriptions but represented 46 percent of all drug spending in the United States. For the average patient who is prescribed a biologic, these drugs cost $10,000 to $30,000 every year (Chen, 2018).

The high cost of biologics has contributed to growing numbers of Americans struggling to afford the medicine they need. One 2022 survey found that one in nine Medicare beneficiaries did not fill a physician's prescription because they could not afford to pay for it (Dusetzina, 2023).

Affording biologics is even harder for patients with expensive medical conditions. High-priced oncology drugs now make up 50 percent to 60 percent of a cancer patient's total costs to treat the illness (Loria, 2022). Once individuals are diagnosed with cancer, more than 40 percent of them spend their entire life's assets to treat their cancer within two years of their diagnosis (Gilligan, 2018).

Over the next several years, the cost of medication is expected to increase even more. One analysis of national health expenditure data from the Centers for Medicare and Medicaid Services (CMS) estimates the total annual cost of drugs in the United States will grow from $564 billion in 2020 to $917 billion by 2030, a 62 percent increase (Roehrig & Turner, 2022).

The FDA Stifles Biosimilar Competition

Patients urgently need solutions to make prescription drugs affordable. The most proven method to lower the cost of prescription drugs is to introduce more generic choices at much lower prices into the prescription drug market. Data from the Food and Drug Administration (FDA) show that introducing a single generic competitor on average reduces drug prices by 39 percent. Two competitors lower prices by 54 percent. Four competitors lower prices by 79 percent. And six competitors lower prices by 95 percent (Conrad, 2019).

Unfortunately, the FDA imposes a burdensome approval process that significantly delays high-quality biosimilars, the generic equivalent of biologics, from entering the market. The FDA regulates biosimilars based on standards established under the Biologics Price Competition and Innovation Act (BPCIA), a provision of the Affordable Care Act (42 USC 262, 2010).

Under this law, when the FDA approves a brand-name biologic to enter the market, it prohibits other drug manufacturers from selling competing biosimilars for 12 years. During this period, the FDA requires that drug companies wishing to sell a competing biosimilar perform lengthy comparative efficacy trials to demonstrate that their drug has

"no clinically meaningful difference" from the brand-name biologic.

After the FDA approves the biosimilar to enter the market, the drug must meet additional requirements for pharmacists to dispense it. The BPCIA requires biosimilars that are intended to be "interchangeable" with biologics to be subject to additional studies to show that patients would not face increased health risks if they switched between the biosimilar and original biologic drug.

This expensive process requires biosimilar makers to spend $100 million to $300 million, from start to finish, to receive FDA approval (Fontanillo, 2022). Unfortunately, growing scientific evidence shows the BPCIA's financially burdensome requirements do not increase the safety or effectiveness of biosimilar drugs (Kirsch-Stefan, 2023). Instead, they raise the cost of developing biosimilars, curtail competition, and raise the price of these important drugs for patients.

The Need for Clinical Efficacy Trials Should Be Revisited

The FDA's most burdensome requirement is the agency's mandate that biosimilar makers perform comparative efficacy trials on their drugs in order to sell them. These clinical trials account for 65 percent of the financial cost of bringing a biosimilar to market (Fontanillo, 2022).

When a drug developer submits an application to the FDA to sell a biosimilar, the agency requires data proving that the drug is highly similar to the original biologic based on "a clinical [efficacy] study or studies (including the assessment of immunogenicity and pharmacokinetics or pharmacodynamics) that are sufficient to demonstrate safety, purity, and potency"(42 USC 262, 2010). Clinical efficacy trials require assembling hundreds of patients with the same medical condition, purchasing large quantities of the original brand-name biologic, and administering the biologic and biosimilar head-to-head to evaluate whether the biosimilar treats the condition as effectively as the brand-name drug (Bielsky, 2020).

However, biosimilar makers already provide the FDA with the information it needs to verify their drug's efficacy before they perform a clinical trial. When a drug maker builds a biosimilar, it purchases large quantities of the original biologic and performs tests known as analytical studies to determine the drug's structure (FDA, n.d.). With this information, the drug maker can rebuild the biologic from scratch.

After drug makers build their own biosimilars, they perform additional tests known as pharmacokinetic (PK) studies. These tests directly evaluate how a person's body responds to a drug—specifically, how the drug is absorbed, distributed, metabolized, and excreted. Through these tests, drug makers can determine if there are any meaningful differences between how patients interact with a biosimilar drug and how patients interact

with its biologic counterpart (Cohen, 2023).

Because these tests can already confirm whether a biosimilar performs as effectively as its biologic counterpart, numerous real-world studies have concluded that comparative efficacy studies are superfluous and unnecessary. One review of clinical trials for 38 biosimilar drugs found that 95 percent of these studies delivered "no value to the scientific review process" to determine if biosimilar drugs performed as effectively as the biologic (Schiestl, 2020). Another review of clinical trials for 20 biosimilar drugs approved in the EU found these studies "did not identify any instance where efficacy trials added crucial information" (Bielsky, 2020).

PK tests are also significantly less expensive to perform, accounting for just 10 percent of the cost of developing a biosimilar (Fontanillo, 2022). PK tests cost less than efficacy studies because they require fewer participants, can be completed with healthy volunteers, and can be completed in less time.

Because PK tests can effectively confirm biosimilarity, the FDA regularly approves drugs based on data gathered from these tests and ignores results from clinical efficacy studies. A 2019 review of biosimilar applications found that the FDA has never rejected a single biosimilar application that passed a PK test but failed its clinical efficacy study (Webster, 2019).

In recent years, the FDA has recognized the superiority of PK tests and has exempted several biosimilars from its requirement to conduct efficacy studies. Since 2020, the agency has waived efficacy study requirements for biosimilar versions of insulin, filgrastim, and pegfilgrastim (Cohen, 2023).

International and global health institutions have also recognized that clinical trials are unnecessary for approving biosimilars. In 2022, the United Kingdom's Department of Health and Social Care issued guidance removing the requirement for comparative efficacy studies (Medicines & Healthcare Products Regulatory Agency, 2022). That same year, the World Health Organization issued guidance stating "pharmacokinetic and pharmacodynamic studies are sufficient to demonstrate biosimilarity" and "large confirmatory efficacy and safety studies are generally not needed" (Kurki, 2022).

Policymakers and the FDA should recognize this growing scientific consensus and base the approval of biosimilars on whether these drugs can pass a PK test. These tests can verify that biosimilars effectively treat patients at a significantly lower cost than clinical trials. Removing the need for clinical efficacy trials for all biosimiliars would dramatically reduce development costs and empower drugmakers to provide these medications at an affordable price.

Longer Exclusivity Delays Biosimilar Competition

Once the FDA determines a biosimilar to be safe and effective, the agency prohibits the drug from entering the market until the original biologic's 12-year exclusivity period expires. The exclusivity period is the duration of time the FDA allows brand-name drugs to compete without generic competition. The FDA enforces exclusivity periods to ensure brand-name drug makers can earn enough profits to recoup the money they invest to invent new drugs.

In contrast, the agency enforces a far shorter five-year exclusivity period for brand-name, small-molecule drugs. When Congress enacted the BPCIA in 2010, the bill's architects believed biologic drugs took longer to develop and required greater financial risks than simpler small-molecule drugs. So in order to encourage drug makers to develop biologics and recoup their research and development investments, they assumed they needed a longer exclusivity period on the market without biosimilar competition.

However, biologic drugs do not require more time to develop than small-molecule drugs. In 2019, a study in *Nature* found biologic and small-molecule drugs take the same amount of time to develop (Beale, 2019). The study's authors evaluated the development time of biologics and small-molecule drugs approved by the FDA between 2007 and 2016. They found both types of drugs take a median of 12.4 years to develop.

Drug makers also do not suffer greater financial risks when they develop biologics rather than small-molecule drugs. On average, biologics have an 18 percent rate of successfully passing the FDA's clinical trials. By comparison, small-molecule drugs have a success rate of just nine percent (Smietana, 2016).

As a result of the BPCIA's mistaken assumptions, the United States now has the longest exclusivity period among industrialized countries for these essential drugs. In Australia and New Zealand, biosimilars can compete with biologics after five years. And in Canada, they can compete after eight years (Beale, 2019).

Allowing biosimilars to compete sooner would save consumers billions of dollars. An analysis by the Blue Cross Blue Shield Association estimates that shortening exclusivity from 12 years to seven years would save Americans $101 billion over a decade, including $23 billion in out-of-pocket costs (Ellis, 2023).

The FDA's Interchangeability Standard Limits Biosimilar Substitution

After the FDA approves a biosimilar to enter the market, the agency imposes additional barriers that limit access to the drug and raise costs. Following approval of a biosimilar, physicians are free to prescribe it, but the FDA imposes severe limits on pharmacists who seek to dispense the drug. While pharmacists may dispense cheaper generic drugs when patients seek to fill a prescription for a non-biologic brand-name drug, the FDA prohibits

pharmacists from dispensing most biosimilars when a patient arrives with a prescription for a biologic (Sacks, 2020).

Under the BPCIA, a pharmacist may substitute a biologic with a biosimilar only if the FDA designates the biosimilar as "interchangeable." For a biosimilar to be considered interchangeable, the BCPIA requires biosimilar makers to prove that patients would not face increased "risk in terms of safety or diminished efficacy" if they alternated between the original biologic and the biosimilar drug during their treatment plan (42 USC 262, 2010). To deliver this evidence, the FDA requires biosimilar makers to perform additional clinical tests known as "switching studies" (FDA, 2019).

The architects of the BPCIA feared that patients would suffer from an immunogenic reaction if they switched between a biologic and a biosimilar. An immunogenic reaction occurs when a person's immune system interprets a medicine's contents to be a foreign substance. In response, the patient's immune system creates antibodies that neutralize the drug's effects. To safeguard against this risk, the BPCIA requires biosimilar makers to conduct switching studies to demonstrate that their drug won't create an immunogenic reaction.

During the switching study, some patients take the original biologic for the entirety of their treatment plans. The rest alternate between the original biologic and the biosimilar. Once it is confirmed that switching between the two medications delivers the same clinical result as taking the original biologic, the FDA approves the biosimilar as interchangeable.

Despite the worries of the BPCIA's authors, patients face virtually zero risks when they alternate between a biologic and biosimilar drug. Since 2006, the European Union has authorized member countries to allow biosimilars to be interchangeable with their biologic counterparts without a switching study. In 2020, European researchers reviewed 178 studies measuring the safety and efficacy of European patients that switched between biosimilars and biologics. Their study found zero evidence that "switching from a reference biological to a biosimilar is related to any major efficacy, safety, or immunogenicity issues" (Barbier, 2020).

As a result of the growing evidence, global health institutions now endorse empowering pharmacists to dispense biosimilars without switching studies. In 2022, the World Health Organization officially recommended that all countries authorize biosimilars to be interchangeable with their biologic counterparts (World Health Organization, 2022). That same year, the European Medicines Agency (EMA) also recommended its member countries allow biosimilars to be interchangeable (European Medicines Agency, 2022).

FDA Hurdles Reduce Competition and Raise Prices

Due to the FDA's costly and unnecessary hurdles, the agency has failed to approve enough biosimilars for these drugs to compete meaningfully with brand-name biologics. As of April 2023, the FDA had approved 671 brand-name biologic drugs (FDA, 2023). However, as of October 2023, the FDA has granted approval to only 43 biosimilar drugs (FDA, 2023). And no biosimilars are in development for 47 percent of biologics that currently lack competition (IQVIA, 2023). Also, the FDA's interchangeability requirements have inhibited the ability of pharmacists to dispense biosimilars. While the FDA has approved 43 biosimilars, it has granted interchangeability to only five (Stewart, 2023).

Expanding the number of biosimilar competitors holds the promise of making biologics significantly more affordable. When biosimilars enter the market, they cost 18 to 50 percent less than brand-name biologic drugs (IQVIA, 2023). In response, biologic makers are compelled to lower their prices or risk losing customers.

Over time, greater biosimilar competition would generate billions of dollars in savings for families, employers, and taxpayers. According to the health company IQVIA, biosimilars are expected to save Americans $125 billion to $237 billion between 2023 and 2027 (IQVIA, 2023). The report noted that how much savings biosimilars actually generate will depend on how many can enter the market and gain greater market share against more expensive brand-name biologics.

Patients who rely on biologic drugs would experience enormous financial relief from these expected savings. Under IQVIA's estimates, the average patient who is prescribed a biologic could save as much as $1,800 to $5,500 every year from greater biosimilar competition. These savings would ensure that many more Americans could afford the medications they need to survive.

Policy Recommendations

Modernizing the FDA's outdated and expensive approval process for biosimilars would bring affordable drugs to the market faster, enhance healthcare access, and improve outcomes for patients. Policymakers should implement the following reforms to ensure patients can purchase low-cost biosimilar drugs without unnecessary delays:

- **Reform clinical efficacy trial requirements:** Lawmakers should remove the requirement that biosimilar makers perform comparative efficacy studies to prove their drug is safe and effective. Instead, the FDA should approve biosimilars based on the results of PK studies and analytical studies.

- **Decrease the exclusivity period for biologics:** Lawmakers should reduce the exclusivity period for biologic drugs instituted by the Biologics Price Competition

and Innovation Act (BPCIA), a provision of the Affordable Care Act. The Fair Care Act (2020) would reduce the exclusivity period for biologics from 12 years to five years. The Trump Administration once proposed decreasing the exclusivity period for biologics from 12 years to ten years as part of the United States-Mexico-Canada Agreement negotiations, and the Obama Administration once proposed a reduction to seven years (Zalewski, et al., 2019).

- **Let pharmacists substitute biologics for biosimilars:** Congress should allow pharmacists to substitute biologics for biosimilars without the need for switching studies. The Biosimilar Red Tape Elimination Act (2023) and the Primary Care and Health Workforce Expansion Act (2023) would empower pharmacists to dispense these important medications.

Conclusion: End Barriers That Stifle Biosimilar Competition

After years of rising prices, it is clear the FDA has failed to approve enough biosimilars to provide robust competition against brand-name biologics. Decades of research show the BPCIA's standards for approving biosimilars do not protect the health and safety of America's patients. Instead, they have worsened the health of families by making biologics increasingly unaffordable and out of financial reach for patients in need.

Patients urgently need solutions from Congress and the executive branch to modernize the FDA's biosimilar approval process. Lawmakers should introduce scientifically sound reforms that maintain high levels of drug safety and efficacy, while also introducing greater biosimilar drug choices. More biosimilar options would increase competition, lower prices, and ensure more families could afford to treat their medical conditions.

Works Cited

Barbier, L., Ebbers, H., Declerck, P., Simoens, S., Vulto, A., Huys, I. (2020). The Efficacy, Safety, and Immunogenicity of Switching Between Reference Biopharmaceuticals and Biosimilars: A Systematic Review. *Clinical Pharmacology & Therapeutics*, 108(4): 734–755. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7540323/#

Beale, R., Hwang, T., Kesselheim, A. (2019). Pre-market development times for biologic versus small-molecule drugs. *Nature Biotechnology*. 37, 708–711. https://www.nature.com/articles/s41587-019-0175-2#:~:text=Median%20total%20pre%2Dmarket%20development,1).

Bielsky, M., Cook, A., Wallington, A., Exley, A., Kauser, S., Hay, J., Both, L., Brown, D. (2020, November). Streamlined approval of biosimilars: moving on from the confirmatory efficacy trial. *Drug Discovery Today*, 25(11): 1910-1918. https://www.sciencedirect.com/science/article/pii/S1359644620303433?via%3Dihub#bib0120

Biosimilar Red Tape Elimination Act, S. 2305, 118th Congress. (2023). https://www.congress.gov/bill/118th-congress/senate-bill/2305?s=1&r=1&q=%7B%22search%22%3A%22S.+2305%22%7D

Chen, B., Yang, YT., & Bennett, C (2018). Why Biologics and Biosimilars Remain So Expensive: Despite Two Wins for Biosimilars, the Supreme Court's Recent Rulings do not Solve Fundamental Barriers to Competition. *Drugs*, 78(17):1777-1781. https://pubmed.ncbi.nlm.nih.gov/30446980/#:~:text=They%20are%20highly%20targeted%2C%20efficacious,for%20the%20most%20expensive%20biologics.

Cohen, H., Turner, M., Dorothy, M., & Woollett, G. (2023, August 5). Future Evolution of Biosimilar Development by Application of Current Science and Available Evidence: The Developer's Perspective. *BioDrugs*, 37, 583–593. https://link.springer.com/article/10.1007/s40259-023-00619-0

Coherent Market Insights. (2022). *Small Molecule Drug Discovery Market, By Therapeutic Area, By Process/Phase, and By Geography - Size, Share, Outlook, and Opportunity Analysis, 2022 – 2028*. https://www.researchandmarkets.com/reports/5669023/small-molecule-drug-discovery-market-by

Conrad, R., Lutter, R. (2019). *Generic Competition and Drug Prices: New Evidence*

Linking Greater Generic Competition and Lower Generic Drug Prices. U.S. Food and Drug Administration. https://www.fda.gov/media/133509/download

Dusetzina, S., Besaw, B., &Whitmore, C (2023). Cost-Related Medication Nonadherence and Desire for Medication Cost Information Among Adults Aged 65 Years and Older in the US in 2022. *Journal of the American Medical Association*, 6(5):e2314211. https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2805012

Ellis, P. (2023, January 24). Savings estimates for options to reduce spending on health care and private insurance premiums. Blue Cross Blue Shield Association. https://www.bcbs.com/the-health-of-america/articles/savings-estimates-options-reduce-spending-health-care-and-private

European Medicines Agency. (2023). *Statement on the scientific rationale supporting interchangeability of biosimilar medicines in the EU.* https://www.ema.europa.eu/en/documents/public-statement/statement-scientific-rationale-supporting-interchangeability-biosimilar-medicines-eu_en.pdf

Fair Care Act of 2020. H.R. 8527, 116th Congress. (2020). https://www.congress.gov/bill/116th-congress/house-bill/8527/text

Fontanillo, M., Kors, B. and Monnard, A. (2022, August19). *Three imperatives for R&D in biosimilars*. McKinsey &Company. https://www.mckinsey.com/industries/life-sciences/our-insights/three-imperatives-for-r-and-d-in-biosimilars

Gilligan, A., Alberts, A., Roe, D., & Skrepnik, G. (2018, June 12). Death or Debt? National Estimates of Financial Toxicity in Persons with Newly-Diagnosed Cancer. *American Journal of Medicine*, 131(10), P1187-1199. https://www.amjmed.com/article/S0002-9343(18)30509-6/fulltext

IQVIA Institute. (2018, April 19). *Medicine Use and Spending in the U.S.A. Review of 2017 and Outlook to 2022*. https://www.iqvia.com/insights/the-iqvia-institute/reports-and-publications/reports/medicine-use-and-spending-in-the-us-review-of-2017-outlook-to-2022

IQVIA Institute. (2023, January 31). *Biosimilars in the United States 2023–2027*. https://www.iqvia.com/insights/the-iqvia-institute/reports-and-publications/reports/biosimilars-in-the-united-states-2023-2027

Kirsch-Stefan, N., Guillen, E., Ekman, N., Barry, S., Knippel, V., Killalea, S., Weise, M., Wolff-Holz, E. (2023, October 13). Do the Outcomes of Clinical Efficacy Trials Matter in Regulatory Decision-Making for Biosimilars?. *BioDrugs*, 37, 855–871.

https://link.springer.com/article/10.1007/s40259-023-00631-4?utm_source=rct_congratemailt&utm_medium=email&utm_campaign=oa_20231013&utm_content=10.1007/s40259-023-00631-4

Kurki, P., Kang, H., Ekman, N., Knezevic, I., Weise, M., Wolff-Holz, E. (2022). Regulatory Evaluation of Biosimilars: Refinement of Principles Based on the Scientific Evidence and Clinical Experience. *BioDrugs*, 36(3): 359–371. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9148871/

Medicines & Healthcare Products Regulatory Agency (2022, November 7). *Guidance on the licensing of biosimilar products*. https://www.gov.uk/government/publications/guidance-on-the-licensing-of-biosimilar-products/guidance-on-the-licensing-of-biosimilar-products

The Primary Care and Health Workforce Expansion Act, 118th Congress. https://www.sanders.senate.gov/wp-content/uploads/Primary-Care-Section-by-Section_07.19.2023.pdf

The Public Health and Welfare Act, 42 U.S.C. 262 (2010). https://uscode.house.gov/view.xhtml?req=(title:42%20section:262%20edition:prelim)

Roehrig, C., Turner, A (2022). *Projections of the Non-Retail Prescription Drug Share of National Health Expenditures*. Altarum. https://altarum.org/publications/projections-non-retail-prescription-drug-share-national-health-expenditures-2022

Sacks, C., Van de Wiele, V., Fuclchino, L. (2020, August 31). Assessment of Variation in State Regulation of Generic Drug and Interchangeable Biologic Substitutions. *Journal of the American Medical Association*. 181(1):16-22. https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/2769770

Schiestl, M., Ranganna, G., Watson, K., Jung, B., Roth, K., Capsius, B., Trieb, M., Bias, P., Marechal-Jamil, J. (2020, April 7). The Path Towards a Tailored Clinical Biosimilar Development. *BioDrugs*, 34, 297–306. https://link.springer.com/article/10.1007/s40259-020-00422-1

Smietana, K., Siatkowski, M., Moller, M. (2016, May 20). Trends in clinical success rates. *Nature Reviews Drug Discovery*, 15, 379–380. https://www.nature.com/articles/nrd.2016.85

Stewart, J. (2023, October 10). *What biosimilars have been approved in the United States?* Drugs.com. https://www.drugs.com/medical-answers/many-biosimilars-approved-united-states-3463281/#bydate

U.S. Food and Drug Administration. (n.d.). *Biosimilar Development Process*. https://www.fda.gov/files/drugs/published/Biosimilar-Development-Process.pdf

U.S. Food and Drug Administration. (2019, May). *Considerations in Demonstrating Interchangeability With a Reference Product*. https://www.fda.gov/media/124907/download

U.S. Food and Drug Administration. (2023, April). *FDA at a Glance*. https://www.fda.gov/media/168049/download

Webster, C., Wong, A., &Woollett, G. (2019). An Efficient Development Paradigm for Biosimilars. *BioDrugs*, 33, 603–611. https://link.springer.com/article/10.1007/s40259-019-00371-4

World Health Organization. (2022, January 27). *The Selection and Use of Essential Medicines*. https://www.who.int/publications/i/item/9789240041134

Zalewski, Z., George, KL., & Diamond, N. (2019). *What's Next for Biologics Under USMCA?* Avalere. https://avalere.com/insights/whats-next-for-biologics-under-usmca