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NATIONAL INSTITUTES OF HEALTH FUNDING, DRUG PRICE NEGOTIATION, AND BIOSIMILARS: THREE FACTORS ESSENTIAL FOR PATIENTS AND PHARMACEUTICAL INNOVATION

Testimony of:

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Summary of major points

- Patients in the US pay more for brand-name prescription drugs than patients in other high-income countries. When patients – especially seniors on Medicare – cannot afford essential medications, they may experience negative clinical outcomes. This committee should consider 3 important steps to support Medicare patients' ability to access essential medicines.
- First, we must protect public investment in scientific research.
  - Nearly all key pharmaceutical innovations in recent decades have relied on substantial public funding from the National Institutes of Health (NIH) and other federal sources.
  - Since inauguration, the rate of new NIH grants has slowed dramatically—falling to less than half the amount awarded during the same timeframe in 2024.
  - Congress must do what it can to restore the normal flow of these funds before the US scientific establishment and the prospects of a new generation of innovative treatments are irreparably damaged.
- Second, we must preserve – and even extend – policies in the Inflation Reduction Act (IRA), which created a process for Medicare to negotiate certain top-selling drugs after being on the market 9-13 years and capped out-of-pocket spending at $2000/year for those with Medicare Part D coverage.
  - Negotiation of the first 10 drugs led to 39-57% price reductions, and negotiations are projected to save the country about $100 billion over the next decade.
  - The EPIC, ORPHAN CURES, and MINI Acts would all delay or exclude numerous lucrative drugs from negotiation and thus reduce savings without offering meaningful benefits to patients or the health care system.
  - Manufacturers have claimed that the IRA violates the Constitution, but these legal arguments lack merit. The government must continue to vigorously defend these provisions in Court.
  - Concerns that the IRA could reduce innovation lack merit: global revenues in the first 9 years following FDA approval for the first group of small-molecule drugs set for negotiation ranged from $14-$57 billion; it is unreasonable to expect that for-profit manufacturers would cease to develop products with the potential for such revenues.
- Third, biologics are among the highest priced drugs, so timely and effective competition from biosimilars—versions of biologics made by other manufacturers—can help promote access to essential medicines.

Subcommittee Chairman Smith, Subcommittee Ranking Member Neal, Committee Chair Buchanan, Committee Ranking Member Doggett, and Members of the Subcommittee:

My name is Aaron Kesselheim. I am an internal medicine physician, lawyer, and a Professor of Medicine at Harvard Medical School, in the Division of Pharmacoepidemiology and Pharmacoeconomics of the Department of Medicine at Brigham and Women's Hospital in Boston, one of the main Harvard teaching hospitals. Within the Division, I lead the Program On Regulation, Therapeutics, And Law (PORTAL), an interdisciplinary research center that studies the intersections between prescription drug affordability and use, the laws and regulations governing medications, and the development and cost of drugs. PORTAL is one of the largest non-industry-funded research centers in the country that focuses on pharmaceutical use, law, and economics. In 2020, I was elected to the National Academy of Medicine.

Prescription drugs and vaccines are among the most effective and cost-effective medical interventions available, and the topic of today's hearing is how Congress can help patients in the US benefit from these products. One of the primary ways they can do so is by ensuring that essential medicines are discovered and developed to treat medical conditions, a process that depends upon public research funding through the National Institutes of Health (NIH) and other federal agencies. But these funds are under attack from the current administration, which threatens to destroy a key source of transformative medical innovation in this country and around the globe. Another way Congress can support patient access to prescription drugs is by helping ensure that they are available at reasonable prices. The Inflation Reduction Act (IRA) took several important measures aimed at promoting prescription drug affordability, including capping out-of-pocket costs for seniors and allowing Medicare to negotiate the prices for certain high-cost drugs. Congress should defend and build on these reforms, rejecting current bills under consideration like the EPIC, ORPHAN CURES, and MINI Acts, which would exclude and delay drugs from negotiation and keep prices excessively high. Finally, Congress can enhance drug affordability by fostering timely and effective biosimilar competition for high-cost biologic therapies.

I. Pharmaceutical Innovation Depends on Research Supported by the National Institutes of Health

The National Institutes of Health (NIH) is the leading global force in the world behind biomedical research and pharmaceutical innovation.[1] The discovery of new medications, vaccines, diagnostics, and other essential interventions typically begins with foundational research, followed by translational studies and proof-of-concept testing in laboratory settings and patients. Countless studies and reports have shown the central role that NIH plays in advancing therapeutic development.[2] Its essential function is recognized

[1] This testimony derives in part from testimony that I previously gave to this Subcommittee on May 10, 2023. See Kesselheim AS. How the government supports meaningful drug and device innovation: funding development of transformative therapies and avoiding excessive prices for new products with limited benefits. Hearing before the House Subcommittee on Health of the Committee on Ways and Means (Rep. Buchanan, Chairman). 11 May 2023. United States Congressional Record. Available on-line at: http://waysandmeans.house.gov/wp-content/uploads/2023/05/Kesselheim-Testimony.pdf

[2] See, e.g., Stevens AJ, Jensen JJ, Wyller K, Kilgore PC, Chatterjee S, Rohrbaugh ML. The role of public-sector research in the discovery of drugs and vaccines. N Engl J Med. 2011 Feb 10;364(6):535-41; Sampat BN, Lichtenberg FR. What are the respective roles of the public and private sectors in pharmaceutical innovation? Health Aff (Millwood). 2011 Feb;30(2):332-9.

around the world[3] and by industry and clinical experts alike.[4] Over two-thirds of Republicans and 90% of Democrats believe that US government investment in fundamental scientific research is worthwhile.[5]

Nearly every drug results from basic scientific discoveries by NIH-funded scientists. A review of drugs approved by the FDA from 2010 to 2016 found that each one could be linked to NIH-supported research.[6] Another study, examining 356 FDA-approved drugs from 2010 to 2019, showed that NIH funding was involved in the development of 354 of them (99.4%), with an average of $1.44 billion in public funding contributing to each approval.[7] Public funding also plays an important role in later stages of drug development, such as initial testing and clinical trials leading to FDA approval. Among drugs approved between 2008 and 2017, 25% (62 out of 248) received contributions from publicly funded research institutions.[8] Additionally, 42% of biologics approved in the same period had late-stage contributions from public-sector institutions or stemmed from public-sector spin-off companies.[9] The role of the government is particularly important in the development of transformative drugs—those that represent groundbreaking innovations with a significant impact on patient care.[10] Drugs with links to late-stage public funding were more likely to be fast-tracked by the FDA or designated as first-in-class, often signifying major therapeutic advancements.[11]

Although private investment is also important for drug development and approval, NIH-funded research focuses primarily on early drug discovery and development when private investment is often lowest due to the high level of risk. These early stages include researching disease mechanisms, identifying modifiable biochemical pathways, isolating novel targets, and developing systems for *in vitro* testing of potential drug

[3] Prescrire International. The important role of public-sector research in the United States. 2013;22(135):54.
[4] See, e.g., Williams RS, Desmond-Hellmann S. Making translation work. Science. 2011;332(6036):1359. ("Academic laboratories have long been ideally suited to unravel the causes of disorders."); Flier JS. Academia and industry: allocating credit for discovery and development of new therapies. J Clin Invest. 2019;129(6):2172-2174. ("Most fundamental biologic insights have resulted from work by academic scientists conducting research to understand how things work, rather than through applied research aiming to produce therapeutic benefits."); Kinch MS, Hoyer D. A history of drug development in four acts. Drug Discov Today. 2015;20(10):1163-8. ("Decreasing NIH funding threatens the future of academia as a source of innovation.")
[5] See, e.g., https://www.pewresearch.org/science/2023/11/14/government-investments-in-scientific-research-and-the-importance-of-the-u-s-being-a-world-leader-in-science/; https://www.researchamerica.org/wp-content/uploads/2025/02/January-2025-National-Survey-Release-2.3.25.pdf
[6] Galkina Cleary E, Beierlein JM, Khanuja NS, McNamee LM, Ledley FD. Contribution of NIH funding to new drug approvals 2010-2016. Proceedings of the National Academy of Sciences of the USA 2018;115(10):2329-2334
[7] Galkina Cleary E, Jackson MJ, Zhou EW, Ledley FD. Comparison of Research Spending on New Drug Approvals by the National Institutes of Health vs the Pharmaceutical Industry, 2010-2019. JAMA Health Forum 2023;4(4):e230511.
[8] Nayak RK, Avorn J, Kesselheim AS. Public section financial support for late stage discovery of new drugs in the United States: cohort study. BMJ 2019;367:15766.
[9] Nayak R, Lee CC, Avorn J, Kesselheim AS. Public-sector contributions to novel biologic drugs. JAMA Internal Medicine 2021;181(11):1522-1525.
[10] Kesselheim AS, Tan YT, Avorn J. The roles of academia, rare diseases, and repurposing in the development of the most transformative drugs. Health Affairs 2015;34:286-294.
[11] See, e.g., Tessema FA, Barenie RE, Avorn J, Kesselheim AS. Federal funding for discovery and development of costly HIV drugs was far more than previously estimated. Health Affairs 2023;42(5):642-649 (finding $143 million in NIH funding helped establish clinical efficacy of tenofovir disoproxil fumarate-emtricitabine (TDF-FTC, or Truvada) for HIV pre-exposure prophylaxis (PrEP)).

candidates.[12] Many large pharmaceutical companies have pulled back from this type of foundational research,[13] making the NIH's contributions even more crucial for the discovery of new treatments. Government funding supported advancements in lipid nanoparticles, mRNA technology, and the SARS-CoV-2 spike protein structure, which enabled rapid understanding of the COVID-19 virus when the recent pandemic struck, and the government then provided a guaranteed market for successful vaccines. These public investments, totalling at least $31.9 billion, played a vital role in the discovery of effective vaccines, which helped protect millions from COVID-19 complications. [14] Virtually all gene and cellular therapies can trace their origins back to NIH funding.[15]

I do not have room in this testimony to detail all the examples of vital pharmaceutical innovations that have resulted from substantial government funding in recent years. NIH funding has played a globally dominant role in advancing therapeutic innovation.

Despite this track record, the current administration has already severely damaged biomedical innovation through cuts at the NIH, CDC, and other federal agencies that support health research. According to a report from the Washington Post, since inauguration day, the pace of federal funds awarded by NIH has slowed dramatically—falling to less than half the level granted during the same timeframe in 2024.[16] The administration is also trying to drastically reduce indirect research funding—by nearly $4 billion per year—to levels below what institutions require to conduct the scientific investigations necessary for medical progress.[17] These funding cuts threaten innovation across all fields of medicine, including HIV[18] and Alzheimer's disease.[19] They will slow or prevent discoveries needed to address conditions that currently lack adequate treatments and may reverse gains made against diseases where NIH-funded

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[12] See, e.g,. Barenie RE, Tessema FA, Avorn J, Kesselheim AS. Public funding for transformative drugs: the case of sofosbuvir. Drug Discovery Today 2021;26(1):273-281 (finding $60.9 million in NIH funding linked to the development of sofosbuvir [Sovaldi] for chronic hepatitis C virus infection, including key work on virus cell culture systems).

[13] https://www.science.org/doi/abs/10.1126/science.aaw2373

[14] Lalani HS, Nagar S, Sarpatwari A, Barenie RE, Avorn J, Rome BN, Kesselheim AS. US Public investment in the development of mRNA COVID-19 vaccines: retrospective cohort study. BMJ 2023;380:e073747.

[15] Vokinger KN, Avorn J, Kesselheim AS. Sources of innovation in gene therapies—approaches to achieving affordable prices. New England Journal of Medicine 2023;388(4):292-295; Newham M, Vokinger KN. Adverse effects of acquisitions in the pharmaceutical industry. Nature Medicine 2022;28(7):1342-1344.

16 Diamond D and Keating D. Trump promised scientific breakthroughs. Researchers say he's breaking science. Washington Post March 28, 2025. ("Since Trump's inauguration on Jan. 20, NIH funding has dropped by more than $3 billion compared with grants issued during the same period last year…an almost 60 percent decline")

17 Badger E et al. How Trump's Medical Research Cuts Would Hit Colleges and Hospitals in Every State. New York Times Feb. 13, 2025 ("[M]any officials at universities and hospitals have said that they may have to pull back on medical or scientific research.")

18 Christensen J. 'People will die based on these decisions': Trump administration cuts funding for dozens of HIV studies. CNN.com. March 25, 2025. ("deep cuts to HIV research grants mean "we would be witnessing innumerable lives lost and destroyed without access to lifesaving discoveries that are a direct result of ongoing HIV innovation and research efforts.'")

19 George J. Alzheimer's Research Caught in Trump Funding Delays. MedPage Today March 26, 2025 ("Funding has effectively been halted at 14 of the nation's 35 [Alzheimer's Disease Research Centers] after the Trump administration repeatedly cancelled NIH advisory council meetings.")

research has delivered meaningful progress.[20] The erosion of funding not only undermines opportunities for scientific discovery in the short-term, but it also threatens advances that could benefit future generations, as young scientists are driven out of research careers in the US.[21]

The devastating impact of these policies on science has been recognized by Democrats and Republicans in Congress alike ,[22] as well as by leaders in academia[23] and industry.[24] NIH funding supports not only medical breakthroughs, but also contributes significantly to the US economy. According to one advocacy organization, "the $36.94 billion awarded to researchers in the 50 U.S. states and the District of Columbia in FY2024 supported 407,782 jobs and $94.58 billion in new economic activity nationwide — or $2.56 for every $1 invested."[25]

For decades, the US government has played a fundamental role in the discovery and development of important new drugs and vaccines through the NIH and other sources of public funding. In the face of a blockade of funds initiated by the Presidential administration and its appointees at the NIH and other agencies, Congress must do whatever it can to re-establish the normal flow of research funds before the US scientific enterprise and the promise of future innovative treatments is irreparably damaged.

II. Provisions in the IRA Help Make Drugs Available to Medicare Patients

Once prescription drugs are approved by the FDA, it is essential that patients have reasonable access to those products. However, high prices have been a major barrier to access for many patients. US policy protects new products from competition for years, and during these periods of monopoly protection there are few checks on the prices manufacturers can charge. Brand-name manufacturers set drug prices in the

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20 Adams R. Trump makes sweeping HIV research and grant cuts: 'Setting us back decades.' The Guardian March 31, 2025 ("the loss of this research could very well result in a resurgence of HIV that becomes more generalized in this country.")

21 Id. ("these drastic cuts are rapidly destroying the infrastructure of scientific research in this country and we are going to lose a generation of scientists"); see also Witze A. 75% of US scientists who answered *Nature* poll consider leaving. Nature March 27, 2025, available at: https://www.nature.com/articles/d41586-025-00938-y (poll of over 1600 scientists find that many are looking for work in Europe and Canada).

22 See, e.g., Hiar C. Universities Reeling from Trump Cuts Fear for a 'Lost Generation' of Scientists. Scientific American March 26, 2025 ("[S]ome GOP senators in states with large research universities are beginning to express concern about Trump's cuts."); Young T and Pottinger M. Funding for R&D isn't a gift to academia: Investing in scientific research and development is vital to U.S. security. Washington Post March 24, 2025. ("The United States' biotechnology innovators, our electronics wizards and our military leaders uniformly point to the importance of a strong science-and-technology ecosystem that starts with the university.")

23 See, e.g., Alladina J, et al. Censored Science Can't Save Lives. NY Times February 18, 2025. ("Censoring research on how to deliver treatments to those most in need isn't just nonsensical; it puts lives at risk and undermines America's leadership in medical innovation.")

24 See, e.g., Gibson C. Recursion CEO: Publicly funded research built the biopharma industry. Now it needs our help. STAT News First Opinion Feb. 19, 2025 ("The NIH and the American government have had a special role to play in funding some of the audacious early science that has made America the leader in biotech and beyond for the past 100 years. While private funds cannot and should not replace the critical funding from the NIH and other public entities, neither can we afford to allow a setback to cut off the flow of early science that has made every single biotech company in the country possible").

25 United for Medical Research. UMR Releases Annual NIH Economic Impact Report: 2025 Update. March 11, 2025. Available at: https://www.unitedformedicalresearch.org/statements/umr-releases-annual-nih-economic-impact-report-2025-update/

US at levels far exceeding prices for the same drugs in other high-income countries.[26] At launch, the median price for a year of treatment with a new drug increased from $2,115 in 2008 to approximately $300,000 in 2023.[27] In addition, manufacturers have frequently raised prices each year on existing drugs, even when there is no new clinical evidence to justify price increases.[28]

As a result of high prices, many Americans struggle to afford their medications. Three in 10 adults who take at least one prescription drug report not taking them as prescribed due to cost.[29] In 2024, 12% of adults over 65 skipped medications due to cost, the highest rate among peer nations.[30] In Medicare, 22% to 50% of patients prescribed high-cost medications for conditions such as cancer and hepatitis C did not initiate treatment with these drugs. Non-adherence to important medications leads to worse clinical outcomes, including increased rates of death.[31]

The consequences of high drug prices extend beyond patient out-of-pocket-costs. The portion of costs not borne directly by patients is ultimately passed on to the public in other ways, including through higher insurance premiums, lower wages as employers absorb these costs, and higher taxpayer spending on public insurance programs like Medicare and Medicaid. Medicaid programs, for example, have been forced to respond to rising prescription drug costs by cutting coverage for other services and limiting access to medications.[32]

In this context, the Inflation Reduction Act of 2022 offered important relief for the health care system by allowing Medicare to directly negotiate prices for certain drugs, just as it already negotiates prices with hospitals, doctors, clinical laboratories, and nearly every other entity that provides goods or services to the Medicare program.[33] Negotiated prices under the IRA will apply only to a limited number of top-selling brand-name drugs that have annual Medicare spending exceeding $200 million and that have been on the

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[26] Mulcahy AW, Whaley CM, Gizaw M, Schwam D, Edenfield N, Becerra-Ornelas AU. International prescription drug price comparisons: current empirical estimates and comparisons with previous studies. ASPE Reports. July 1, 2022. Available at: https://aspe.hhs.gov/reports/international-prescription-drug-price-comparisons

[27] Rome BN, Egilman A, Kesselheim AS. Trends in prescription drug launch prices, 2008-2021. JAMA 2022;327(21):2145-2147**;** Beasley D. Prices for new US drugs rose 35% in 2023, more than the previous year. Reuters. February 23, 2024.

[28] Egilman AC, Kesselheim AS, Rome BN. Estimated Medicare Part B savings from inflationary rebates. JAMA 2023;329(1):89-92; see also https://icer.org/wp-content/uploads/2023/04/UPI_2023_Report_121123.pdf.

[29] Sparks G, et al. Public opinion on prescription drugs and their prices. Kaiser Family Foundation. October 4, 2024. Available at: https://www.kff.org/health-costs/poll-finding/public-opinion-on-prescription-drugs-and-their-prices/ ("majorities see these drugs as too expensive and three in ten struggle to afford their medicines")

[30] https://www.commonwealthfund.org/publications/issue-briefs/2024/dec/health-care-affordability-older-adults-how-us-compares-other-countries

[31] Gagne JJ, Choudhry NK, Kesselheim AS, Polinski JM, Hutchins D, Matlin OS, Brennan TA, Avorn J, Shrank WH. Comparative effectiveness of generic and brand-name statins on patient outcomes. Annals of Internal Medicine 2014;161:400-407.

[32] Galewitz P. States cut Medicaid drug benefits to save money. Kaiser Health News July 24 2012. Available at: https://khn.org/news/medicaid-cuts-sidebar/

[33] This testimony derives in part from testimony that I previously gave to the Energy and Commerce Committee on September 20, 2023. See The Inflation Reduction Act of 2022: reducing excessive spending and Supporting patient access to brand-name drugs while promoting meaningful innovation. Hearing before the House Subcommittee on Oversight and Investigations of the Committee on Energy and Commerce (Rep. Griffith, Chairman). 20 September 2023. United States Congressional Record. Available on-line at: https://energycommerce.house.gov/events/oversight-and-investigations-subcommittee-hearing-1

market for at least 9 years (13 years for biologic drugs). Certain drugs, , such as those approved exclusively for a single rare disease, are exempt from negotiation. In its negotiations, CMS must consider multiple factors, such as whether the drug represents an important therapeutic advance or fulfills an unmet medical need, whether the manufacturer has recouped its research and development costs, and the degree to which federal funding contributed to its discovery.[34] The legislation imposes upper bounds on the negotiated price: for drugs on the market for 9-16 years, the maximum negotiated price is 75% of the non-federal average manufacturer price; for drugs older than 16 years, that cap drops to 40%. In exchange, once a negotiated price is finalized, all Part D plans are required to cover the drug on their formularies.[35] Negotiated prices remain in effect until there is direct competition from a generic or biosimilar version. The IRA also provides for the possibility of price renegotiation if a material change occurs, such as approval of a new indication.[36]

The Congressional Budget Office (CBO) estimated that over the next decade, Medicare will save approximately $98.5 billion as a result of these negotiations.[37] While these are savings to the federal government, a portion of savings were appropriated to lower medication costs for patients with Medicare prescription drug coverage, including capping annual out-of-pocket spending to $2000 starting in 2025,, limiting insulin costs to $35 per month, eliminating out-of-pocket costs for vaccines, andnexpanding the low-income subsidy to ensure it can benefit patients near the federal poverty level. Medicare price negotiations are widely popular among the public; over three quarters of republicans and 90% of democrats support allowing Medicare to negotiate prescription drug prices.[38]

The outcomes of the first round of negotiations have been promising. According to the Department of Health and Human Services (HHS), negotiated prices for the first group of 10 drugs reflect discounts ranging from 38% to 79% compared to manufacturer list prices. If those negotiated prices had been in place in 2023, the government would have saved $6 billion, even after accounting for discounts negotiated by private Part D plans. Notably, these negotiated prices were still higher than the prices paid for the same drugs in comparable high-income countries, suggesting that they offer continued meaningful revenues for manufacturers.[39] These figures reflect the potential for real, tangible savings under the IRA. However, these initial figures only scratch the surface of what could be achieved. One analysis of drugs expected to be negotiated in 2026-2028 found that they accounted for $67.4 billion—or 33.9% —of gross Medicare spending in 2020 and treated conditions such as diabetes, cancer, and cardiovascular disease, suggesting significant savings and out-of-pocket cost reductions may be achievable for common chronic conditions.[40]

Despite the successful first round of negotiations based on a reasonable set of factors that led to meaningful—but not punitive—price reductions, the pharmaceutical industry has filed numerous lawsuits

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[34] Hwang TJ, Kesselheim AS, Rome BN. New reforms to prescription drug pricing in the US: opportunities and challenges. JAMA 2022;328(11):1041-1042.
[35] Id.
[36] Id.
[37] Congressional Budget Office. Cost estimate. Sept 7, 2022. https://www.cbo.gov/system/files/2022-09/PL117-169_9-7-22.pdf.
[38] https://www.kff.org/health-costs/poll-finding/public-opinion-on-prescription-drugs-and-their-prices/
[39] Rome BN, Kesselheim AS, Feldman WB. Medicare's first round of drug-price negotiation – measuring success. New England Journal of Medicine 2024;391(20):1865-1868.
[40] Dickson S, Hernandez I. Drugs likely subject to Medicare negotiation, 2026–2028. Journal of Managed Care and Specialty Pharmacy 2023;29(3):229–235.

claiming that the negotiation program is unconstitutional. These lawsuits lack merit. For example, pharmaceutical manufacturers and their lawyers have argued that the IRA violates the Takings Clause, which prohibits the taking of private property for public use without just compensation. But private entities have no legal right to receive taxpayer dollars or to unilaterally set their own reimbursement rates.[41] The IRA attempts to level the playing field by allowing Medicare to negotiate prices, as it already does for nearly every other good and service it purchases, and just like any other market participant purchasing health services. Although manufacturers own the drugs they produce they do not have a constitutionally protected right to taxpayer-funded reimbursement. Another of the manufacturers' legal arguments is that the Act is an unlawful delegation of authority to CMS, but the IRA provides clear statutory guidance and limits on CMS's authority, from defining which drugs are eligible for negotiation to specifying the procedures for conducting the negotiations.

In addition to these meritless legal arguments, pharmaceutical manufacturers have sought to undermine the negotiation program by supporting legislation that would exclude many more drugs from negotiation - drastically undercutting the savings that patients and the health care system can expect in the future.

Perhaps the most destructive proposal is the EPIC Act (H.R. 1492), which would delay price negotiation for small-molecule drugs by an additional 4 years, aligning their eligibility timeline with the current 13-year minimum market period required for biologic drugs to qualify for negotiation. The claimed justification for this change is to achieve "parity"[42] and eliminate the so-called "small molecule penalty,"[43] which purportedly disfavors investment in small molecule drug innovation vs. biologics. But the bill would not achieve parity, while undercutting the negotiation program, leaving Medicare patients exposed to excessively high prices for longer periods of time. First, analyses show that small molecule and biologic drugs have comparable development times and costs, while biologics have generated higher revenues and maintained longer market exclusivity periods.[44] These factors—not the IRA—have driven the shift in manufacturer investment toward the development of biologic drugs over the past twenty years. All of this raises legitimate questions about whether biologic drugs need an additional 4 years of protection from price negotiation beyond what is afforded to small-molecule drugs. If advocates were genuinely seeking parity between the two drug categories, a more sensible policy would be to shift the timeline for biologics earlier—not to delay small molecules further (in nearly every other country that negotiates drug prices, negotiation begins immediately after approval). The pharmaceutical industry has erroneously equated the timing of price negotiation eligibility with the "patent cliff" marking the end of market exclusivity and entry of generic/biosimilar competition, but as the negotiated prices for the first 10 drugs demonstrate, negotiation allows manufacturers to continue to earn substantial revenue from Medicare sales.

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41 "[A] long line of cases instructs that no taking occurs where a person or entity voluntarily participates in a regulated program or activity." Baker County Medical Services Inc v. Attorney General, 763 F.3d 1274, 1276 (11th Cir. 2014).

42 Clifford KA, Levine AA, Enright DE, Neumann PJ, Chambers JD. Small-Molecule Drugs Offer Comparable Health Benefits to Biologics at Lower Costs. Health Affairs 2024;43(11):1546-1552.

43 Stanford J. Congress must fix the IRA's small molecule penalty. STAT First Opinion. March 6, 2023. Available at: https://www.statnews.com/2023/03/06/congress-must-fix-ira-small-molecule-penalty/

44 See, e.g., Wouters OJ, Vogel M, Feldman WB, Beall RF, Kesselheim AS, Tu SS. Differential Legal Protections for Biologics vs Small-Molecule Drugs in the US. JAMA. 2024;332(24):2101-2108; Rome BN, Lee CC, Kesselheim AS. Market Exclusivity Length for Drugs with New Generic or Biosimilar Competition, 2012-2018. Clin Pharmacology and Therapeutics 2021;109(2):367-371.

Second, despite the revenue potential of biologic drugs, small molecule drugs have remained a target of drug development. Biologic drugs are often more complex to manufacture and distribute than small molecule drugs, making them less attractive to certain companies. Biologic drugs also frequently require intravenous administration, which can be less appealing to patients—particularly for diseases for which small molecule alternatives exist. Finally, biologic drugs are not able to reach every potential disease target or pathway, particularly because they can be too large to cross the blood-brain barrier, limiting their usefulness for neurological conditions.

Finally, it is worth recognizing that investment in small-molecule drugs can be extremely lucrative. Among the first 10 drugs selected for price negotiation, global revenues for the 7 small molecule drugs in their first 9 full years after FDA approval ranged from approximately $15 billion to $57 billion *per drug*.[45]

For all of these reasons, the IRA does not endanger the future of small molecule drug innovation. What the EPIC Act would do, however, is delay Medicare negotiation for small molecule drugs from 9 to 13 years resulting in billions of dollars in unnecessary spending on treatments for cancer, HIV, hepatitis C, and other serious conditions. If the EPIC Act were in place today, several drugs eligible to be selected for Medicare negotiation in 2026 and 2027 would be subject to delays including the HIV treatment bictegravir/emtricitabine/tenofovir alafenamide (Biktarvy), which had cumulative earnings of over $45 billion by its seventh year on the market. Other affected drugs would likely include the cancer drugs apalutamide (Erleada), abemaciclib (Verzenio), and venetoclax (Venclexta), and the hepatitis C antiviral sofosbuvir/velpatasvir (Epclusa). Cumulative net sales within the first 6 years after FDA approval for each of these products far surpassed even the most generous estimates of their research and development costs. Delaying price negotiation for these top-selling drugs would amount to a government hand-out to pharmaceutical companies, at the direct expense of Medicare and its beneficiaries.

Since negotiation is designed to arrive at fair prices based on a drug's clinical value, the optimal time to begin negotiation is shortly after FDA approval. Negotiating drugs after approval would still allow manufacturers to earn substantial revenues from important new drugs that address unmet medical needs, while encouraging investment in the most innovative and effective new treatments rather than in derivative products that offer little improvement over existing options.

Another problematic proposal is the ORPHAN Cures Act (H.R. 946), which would expand the IRA's "sole orphan" exclusion to include drugs FDA-approved for "one or more" rare disease indications ("multi-orphans"). But multi-orphan drugs that qualify for IRA negotiation are *extremely profitable*—potentially even more so than sole-orphan products. We found that between 2012 and 2021, Medicare spent $108 billion dollars on 20 multi-orphans that would have qualified for Medicare negotiation.[46] The median multi-orphan drug had $746 million in peak annual Medicare expenditures, far higher than the $567 million median for sole-orphan drugs. Under the ORPHAN Cures Act, nearly 10% of Medicare drug spending-between the sole orphan and multi-orphan drugs would be off the table for price negotiation.

The stated reason for the ORPHAN Cures Act is to eliminate a potential disincentive: that manufacturers of a rare disease drug might forgo seeking approval for additional rare disease indications out of concern it

[45] Results compiled through 2022 using global revenue data. Entresto only contributed 7.5 years of data and Jardiance 8.5 years. This is a conservative estimate, since the numbers are not adjusted for inflation.
[46] Vogel M, Zhao O, Feldman WB, Chandra A, Kesselheim AS, Rome BN. Cost of exempting sole orphan drugs from Medicare negotiation. JAMA Internal Medicine 2024;184(1):63-69.

would make it eligible for price negotiation. But it would be ethically dubious for a manufacturer to avoid developing a drug for additional rare disease populations for fear of qualifying for an IRA negotiation process that achieves a moderate price reductions 9-13 years after launch. But assuming manufacturers in such circumstances will prioritize maximizing profits over promising treatments for patients with rare diseases, manufacturers could still conduct clinical trials for additional patient populations while foregoing FDA approval. They could then rely on off-label use of their drugs, which is often reimbursed by payors for patients with rare diseases, particularly when supported by high-quality evidence.

A better policy choice would be to eliminate the sole-orphan exemption altogether and allow Medicare to negotiate prices for drugs approved to treat a single Orphan Drug Act-designated disease. The IRA already protects low-revenue drugs by excluding them from negotiation. Moreover, drugs for rare diseases are not less lucrative than drugs for more common conditions. We found that drugs initially approved for an Orphan Drug Act-designated condition had median 5-year net sales of $719 million, compared to $812 million for nonorphan drugs.[47] For the 10 sole-orphan rare disease-designated drugs that could become eligible for price negotiation under the IRA in the coming years, the actual and projected revenues ranged from $4 billion to $72 billion in the years before they would face price negotiation under the IRA framework. Thus, eliminating the sole-orphan drug exemption would allow Medicare to negotiate fairer prices for these profitable drugs, yielding additional savings for patients and taxpayers. It would also remove any hypothetical disincentive for seeking additional indications for existing rare disease drugs.

The other major provision in the ORPHAN Cures Act would change the timing of Medicare drug price negotiation for drugs initially approved for a rare disease and subsequently approved for non-rare diseases such that the clock for IRA negotiation eligibility (9 or 13 years) would start based on the approval for the non-rare disease, not the drug's original approval date. This amendment would greatly undermine the savings and patient benefits derived from Medicare drug price negotiation. Among the top-selling drugs that would have qualified for negotiation had the IRA been in effect in 2012-2023, 13 were first approved for rare diseases and later received additional approvals for non-rare conditions. There was a median of about 2 years (interquartile range: 1.2-7.3 years) between the rare disease approval and the subsequent non-rare disease approval, although the time differential was as high as 15.5 years in the case of epoetin alfa (Epogen) for anemia associated with end-stage renal disease.[48] Together, these 13 drugs accounted for $75 billion in Medicare spending from 2012-2021 *alone*. Delaying the negotiation of these drugs would considerably reduce savings expected from the IRA without any reasonable justification, since these drugs are already extremely lucrative for their manufacturers.

Finally, the MINI Act (H.R. 1672) would delay Medicare drug price negotiation by 4 years for small-molecule drugs classified as "advanced drug products," defined as a drug that "incorporates or utilizes a genetically targeted technology … that may result in the modulation (including suppression, up-regulation, or activation) of the function of a gene or its associated gene product." But this definition is overly vague. Which drugs would qualify? For example, would this exclusion apply to products like ibrutinib (Imbruvica), a Bruton tyrosine kinase inhibitor treatment for cancers like chronic lymphocytic leukemia that qualified in the first year of IRA negotiation? While ibrutinib is not a non-replicating nucleic acid, it may be considered an analogous compound under this vague language, as it is genetically targeted in that it inhibits the Bruton tyrosine kinase from promoting cell differentiation and growth. Yet ibrutinib

[47] Tu SS, Nagar S, Kesselheim AS, Lu Z, Rome BN. Five-year sales for newly marketed prescription drugs with and without initial Orphan Drug Act designation. JAMA 2023;329(18):1607-1608.
[48] https://www.biopharmadive.com/news/amgen-enbrel-patent-thicket-monopoly-biosimilar/609042/

generated over $45 billion in its first 9 years on the market – a value that far exceeds any reasonable projection of its development costs and would have clearly been a target for investment even with the possibility of Medicare negotiated prices after 9 years.

III. Biosimilars

A key strategy to help ensure patients benefit from affordable drug prices is by promoting timely and effective competition from generic medications (for small-molecule brand-name drugs) and biosimilars (for biologics). While biologics account for only 2% of prescriptions in the US, they represent about half of prescription drug spending.[49] To address these high costs, the Biologics Price Competition and Innovation Act (BPCIA) established a streamlined process for the FDA to approve biosimilars, which are biologics produced by different manufacturers with no clinically significant differences from already-approved biologic drugs. However, in the first decade following the BPCIA's enactment, the introduction of biosimilar competition faced approval delays, slow adoption, smaller-than-anticipated cost savings, and inconsistent savings for patients.

Fortunately, the impact of biosimilars on the US market has improved over time. For example, biosimilars for the top-selling drug in the world, adalimumab (Humira) entered the US first in January 2023. We found that in the first year of adalimumab biosimilar competition, biosimilars made up fewer than 2% of prescriptions in the US, but there was a nearly 50% decrease in adalimumab net spending and prices, likely due to substantial rebates negotiated by health plans and pharmacy benefit managers.[50]

One potential reason why the biosimilar market has been so sluggish in the US is a lack of easy substitution between the original biologic and its biosimilars. For small molecule drugs, pharmacy substitution is a major source of savings, but until recently, most biosimilars have been approved through the BPCIA as being highly similar, but not interchangeable. As a result, biosimilars must be specifically requested by the prescriber, rather than being dispensed if available at the pharmacy, as generic drugs are. Recently, the FDA's criteria for biosimilar interchangeability have evolved, and some at the agency have suggested eliminating the separate interchangeability designation altogether.

Enhancing biosimilar interchangeability with its reference product could help boost biosimilar adoption in the US, but additional measures could further increase savings for patients and the health care system. These include addressing state laws that prevent pharmacists from automatically substituting biologics with a biosimilar, ensuring pharmacy benefit managers do not unduly favor original biologics over biosimilars on formularies, and improving outreach and education to patients and healthcare providers to alleviate concerns about biosimilars. At the same time, Congress should advance laws that ensure the long-term affordability of biologic drugs, such as making it harder for manufacturers to build large thickets of biologic patents that block timely biosimilar entry, enacting restrictions on pharmaceutical benefit manager drug rebate flexibilities to enhance insurer coverage of lower-cost biosimilar drugs, and changing CMS rules to allow common billing codes for biologics and biosimilars.

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[49] Association for Accessible Medicines. 2023 Generic and Biosimilar Medicines Savings Report. Available from: https://accessiblemeds.org/sites/default/files/2023-09/AAM-2023-Generic-Biosimilar-Medicines-Savings-Report-web.pdf

[50] Rome BN, Bhaskar A, Kesselheim AS. Use, Spending, and Prices of Adalimumab Following Biosimilar Competition. JAMA Health Forum 2024;5(12):e243964.