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**ADDRESSING PHARMACEUTICAL PATENT ABUSES
COULD LOWER DRUG SPENDING AND IMPROVE PATIENT OUTCOMES**

Testimony of:

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Summary of major points

- Largely driven by high-priced brand-name drugs, prescription drug spending in the US jumped from \$427 billion in 2015 to \$511 billion in 2019. The only source of meaningful competition that lowers drug spending in the US right now comes from generic drugs and biosimilars that emerge after brand-name drugs' market exclusivity periods end.
- In the US, two sources of law set a brand-name drug's market exclusivity period. The first are statutes that prevent the FDA from approving competing generics or biosimilars for set periods of time ("regulatory exclusivity"). The second is the Patent Act, which authorizes the government to issue patents—20-year monopoly periods—that cover new drugs.
 - Overall, brand-name small molecule drugs have received an average of about 14.4 years of market exclusivity, while brand-name biologic drugs have received about 21.5 years in the US.
- Patent and regulatory exclusivities were originally designed to provide an incentive and reward for investment in drug development by allowing investors and manufacturers to profit for a finite amount of time. But this system has become subject to many abuses, as brand-name manufacturers take numerous steps to try to extend their market exclusivity as long as possible.
- One of the most common and effective strategies that manufacturers use to delay generic or biosimilar competition is by obtaining a thicket of additional patents on their drugs, beyond the key patent on the underlying active ingredient. These patents may have been improperly granted because they lack novelty or only cover minor, obvious changes to the drug or its delivery device.
 - Improper drug patents can be overturned by litigation initiated by generic or biosimilar manufacturers, but such litigation can take a long time and requires substantial resources, and sometimes leads to settlements in which the patents remain in force.
 - In the case of adalimumab, 247 patent applications have been filed in the US, leading to 105 additional granted patents beyond the primary patent. After litigation over dozens of these patents, biosimilar manufacturers in settlements agreed to remain off the US market until 2023, although they were allowed to sell their products in most countries in the European Union as soon as October 2018, leading to billions of dollars in excess spending in the US.
- There are a number of ways to protect and reward innovation fairly, yet ensure that there is timely entry of generic and biosimilar drugs after the end of a reasonable period of market exclusivity.
 - Low-quality patents should not be granted in the first place. One way to do that would be to allocate greater resources to the US Patent and Trademark Office to promote patent quality.
 - Another solution is to use more efficient pathways to overturn inappropriately granted drug patents before they become caught up in litigation and become the basis of brand/generic or brand/biosimilar settlements. One way to do that would be to ensure that the Patent Trial and Appeals Board, an administrative process established in 2011, reviews all drug patents listed with the FDA or that are brought forward in biosimilar litigation.
 - We can also take steps to ensure that manufacturers cannot use other statutory regulatory exclusivity periods to improperly delay entry of generic or biosimilar drugs, like the one created by the Orphan Drug Act.
- Granting government-protected monopoly status to prescription drugs through exclusivity rights was designed to protect and reward innovation, but "gaming the system" can make it more lucrative for a drug company to fend off generic competitors rather than come up with important new discoveries that will benefit patients. This bloats health care costs and puts medication prices out of the reach of many patients. We need policy changes to ensure timely and efficient availability of generic and biosimilar competition after reasonable periods of market exclusivity; this will help contain our highest-in-the-world drug prices and actually improve meaningful drug innovation.

Chairman Maloney, Ranking Member Comer, and Members of the Committee:

My name is Aaron Kesselheim. I am an internal medicine physician, lawyer, and health policy researcher 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. I lead its Program On Regulation, Therapeutics, And Law (PORTAL), an interdisciplinary research group that studies the intersections between prescription drug affordability and use, laws and regulations related to 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 law, use, and economics. I am honored to have been invited today to talk to you about what can be done to curb abuses by some manufacturers that take advantage of our market exclusivity system for prescription drugs, raising the prices for their products and jeopardizing patient outcomes.

I will review how the US regulates market exclusivity for prescription drugs, and how these protections are sometimes stretched past their limits by drugmakers to increase their profits by unfairly delaying generic or biosimilar competition. I will then discuss potential reforms that can help ensure timely and effective competition in the US market, which would benefit patients and the health care system.

I. Spending on Prescription Drugs in the US: Brand-Name vs. Generic/Biosimilar Drugs

The process of drug discovery and development can take many years and cost a lot of money. Public funding plays a major role in this process, both in the basic and translational research that identifies targets for drug innovation and in the later-stage proof-of-concept and clinical testing of investigational products.¹ Of course, venture capitalists and pharmaceutical manufacturers also spend substantial resources on drug development, and provide most of the expenses associated with clinical trials, regulatory approval, and manufacturing of new products.² The law is designed to reward this private investment in drug development by providing a period of market exclusivity for approved drugs during which manufacturers can charge prices well beyond the cost of production, to reimburse their expenses and provide profits. A company gives its new drugs a brand name and markets them widely during this period around the world. It has been estimated that large pharmaceutical manufacturers spend about \$30 billion a year in drug promotion,³ and the percent of revenues they spend on marketing and administration eclipses the amount allocated to research and development (10-20%).⁴ In the US, drug marketing is also done through direct-to-consumer ads. The US and New Zealand are the only two industrialized countries that allow unfettered direct-to-consumer advertising of brand-name drugs.

Largely driven by spending on brand-name drugs during these periods of government-granted market exclusivity, prescription drug spending in the US jumped from \$427 billion in 2015 to \$511 billion in 2019.⁵ This is far more per capita than any other industrialized nation; the US per-capita pharmaceutical spend of \$1228 per year is more than double that of other wealthy countries, which averaged \$562 in

¹ See e.g., 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; 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; Nayak RK, Avorn J, Kesselheim AS. Public support for late-stage new drug discovery; cohort study. *BMJ* 2019;367:l5766

² Moses H 3rd, Matheson DH, Cairns-Smith S, George BP, Palisch C, Dorsey ER. The anatomy of medical research: US and international comparisons. *JAMA* 2015;313(2):174-189.

³ Schwartz LM, Woloshin S. Medical marketing in the United States, 1997-2016. *JAMA* 2019;321(1):80-96.

⁴ Kesselheim AS, Avorn J, Sarpatwari A. The high cost of prescription drugs in the United States: origins and prospects for reform. *JAMA* 2016;316(8):858-871.

⁵ Tichy EM, Schumock GT, Hoffman JM, et al. National trends in prescription drug expenditures and projections for 2020. *American journal of health-system pharmacy*. 2020;77(15):1213-1230.

2018.⁶ Even though brand-name drugs make up only about 10% of all filled prescriptions in the US, they account for over three-quarters of drug spending. This is because the US is the only country in which drugmakers can set any price they choose for new patented products. New drugs are launched by their manufacturers at extremely high prices; those prices are then regularly subject to annual price increases that can go well beyond the rate of inflation during their years of market exclusivity.⁷ As a result, the highest-priced drugs leading to the most spending in the US are often ones that have been on the market for many years. For example, in 2019, the top three drugs accounting for the greatest spending in Medicare’s outpatient prescription drug insurance program for patients over age 65 were the anticoagulants apixaban (Eliquis), which has been on the market for 8 years, and rivaroxaban (Xarelto), on the market for 10 years, and the cancer treatment lenalidomide (Revlimid), which has been on the market for 15 years. These three drugs alone accounted for about \$16 billion in gross spending for Medicare just in 2019, or about \$10 billion in net spending after accounting for estimated rebates from manufacturers. In Medicare Part B—which covers hospital- or physician-administered drugs for patients over 65—the top-spending drugs in 2019 included the ophthalmologic drug aflibercept (Eylea, \$2.9 billion total spending, 9 years on market) the anticancer drug rituximab (Rituxan, \$1.7 billion, 23 years), and pegfilgrastim (Neulasta, \$1.2 billion, 19 years). During these years of government-granted market exclusivity, the lack of the ability to negotiate prices allows manufacturers to price drugs at whatever level they want and then raise their prices annually without restraint, with only a few exceptions.⁸

Increases in brand-name drug prices directly translate to higher out-of-pocket costs for many patients; in one recent study led by Dr. Benjamin Rome in our Division, among patients who paid any drug deductible or coinsurance, increases in brand-name drug list prices were correlated with changes in their out-of-pocket spending.⁹ High brand-name drug prices have important implications for patients. In national surveys, Americans report challenges in affording their prescriptions, with many reporting not taking a medication as prescribed because of the cost.¹⁰ High prices can lead patients to skip doses or take lower doses than prescribed, which can lead to worse health outcomes as well as costly and preventable medical complications. In one study, patients prescribed costly brand-name cholesterol-lowering medications instead of lower-cost versions were found to have higher rates of cardiovascular death, likely due to non-adherence.¹¹ Drug spending accounts for a bit less than 20% of overall health care spending, but spending in this area also affects other health care and social spending, since funds used for prescription drugs are not available to meet other needs. Medicaid programs, for example, have responded to expanding drug budgets by cutting coverage for other services and limiting access to drugs.¹²

⁶ Kesselheim AS, Hwang TJ, Avorn J. Paying for Prescription Drugs in the New Administration. *JAMA* 2021;325(9):819-820.

⁷ Raimond VC, Feldman WB, Rome BN, Kesselheim AS. Why France spends less than the United States on drugs: a comparative study of drug pricing and pricing regulation. *Milbank Quarterly* 2021;99(1):240-2721.

⁸ See, e.g., Sarpatwari A, DiBello J, Zakarian M, Najafzadeh M, Kesselheim AS. Competition and price among brand-name drugs in the same class: a systematic review of the evidence. *PLoS Medicine* 2019;16(7): e1002872; Sarpatwari A, Tessema FA, Zakarian M, Najafzadeh MN, Kesselheim AS. Diabetes drugs: list price increases were not always reflected in net price; impact of brand competition unclear. *Health Affairs* 2021;40(5):772-778.

⁹ Rome BN, Feldman WB, Desai RJ, Kesselheim AS. Correlation between changes in brand-name drug prices and patient out-of-pocket costs. *JAMA Network Open* 2021;4(5):e218816.

¹⁰ “Three in ten of all adults (29 percent) also report not taking their medicines as prescribed at some point in the past year because of the cost.” Kirzinger A, Munana C, Wu B, Brodie M. Data Note: Americans’ Challenges with Health Care Costs. KFF. 2019. <https://www.kff.org/health-costs/issue-brief/data-note-americans-challenges-health-care-costs/>. 11 June 2020.

¹¹ 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.

¹² Galewitz P. States Cut Medicaid Drug Benefits to Save Money. *Kaiser Health News* July 24 2012. <https://khn.org/news/medicaid-cuts-sidebar/>

When the market exclusivity periods end, meaningful competition can begin. This comes from generic drugs for “small-molecule” medicines like atorvastatin (Lipitor) and fluoxetine (Prozac), and biosimilars for biologic drugs such as monoclonal antibodies and other proteins like adalimumab (Humira), one focus of today’s hearing. Both generics and biosimilars are FDA-approved versions of the original product that are made by different manufacturers; they contain the same active ingredient and have been shown to be comparable to the original version. In nearly all cases, FDA-approved generic and biosimilar products are also clinically equivalent, and patients can be reassured that they are as safe and effective as the brand-name versions.¹³ Generics and biosimilars are usually less expensive than the brand-name version because of competition; the idea behind our nation’s patent system, dating back to the Constitution, is that a period of exclusivity enables innovators to profit from their creation, and then allows others to compete once that period is over, to prevent a permanent monopoly. This is especially important for medications. Crucially, interchangeable generic drugs can be automatically substituted for brand-name versions and for each other at the pharmacy counter.¹⁴ As a result, spending on a given small-molecule drug can fall quickly after the introduction of generics to the market. In a different study also led by Dr. Rome, we found that within a year after a generic drug reaches the market, generics accounted for about two-thirds (66%) of all prescribing, which rose to 83% by the second year after generic entry.¹⁵ In a study led by Dr. Chintan Dave in my research group, we found that the generic price for a given drug was 15-20% lower than the brand-name price when there were just 1-2 market entrants; this went up to reductions of 70-80% when there were 8 or more market entrants.¹⁶ The FDA has not yet approved the automatic interchangeability of biosimilar drugs, but biosimilars have led to major price reductions in Europe, where biosimilars are much more widely available and prices are in many countries directly negotiated by the government. Even without interchangeability, important price reductions have been observed in the US. In one review of biosimilars for 7 products led by my colleague Dr. Richard Frank at Harvard Medical School, we found that prices have fallen meaningfully as competition has intensified in the US: each additional biosimilar entrant to the market was associated with a reduction in average market prices of between 4 and 10 percent.¹⁷

II. Market Exclusivity: Patents and Other Protections for Brand-Name Drugs

In the US, two sources of law determine the length of the market exclusivity period. The first are statutes that prevent the FDA from approving competing generics or biosimilars for set periods of time; this is sometimes called “regulatory exclusivity” because they serve to block approval of competition. The second is the Patent Act, which authorizes the government to issue patents—20-year monopoly periods—that cover new drugs.

¹³ See, e.g., Kesselheim AS, Misono AS, Lee JL, Stedman MR, Brookhart MA, Choudhry NK, Shrank WH. The clinical equivalence of generic and brand-name drugs used in cardiovascular disease: a systematic review and meta-analysis. *JAMA* 2009;300:2514-2526; Kesselheim AS, Stedman MR, Bubrick EJ, Gagne JJ, Misono AS, Lee JL, Brookhart MA, Avorn J, Shrank WH. Seizure outcomes following use of generic vs. brand-name antiepileptic drugs: a systematic review and meta-analysis. *Drugs* 2010;70(5):605-621.

¹⁴ Sacks CA, van de Wiele VL, Fulchino LA, Patel L, Kesselheim AS, Sarpatwari A. Assessing variation in state regulation of generic drug and interchangeable biologic substitution. *JAMA Internal Medicine*. Published online August 31, 2020

¹⁵ Rome BN, Lee CC, Gagne JJ, Kesselheim AS. Factors associated with generic drug uptake in the US, 2012-2017. *Value in Health* 2021. Available from: <https://www.sciencedirect.com/science/article/abs/pii/S1098301521001078>.

¹⁶ Dave CV, Hartzema A, Kesselheim AS. Prices of generic drugs associated with numbers of manufacturers. *New England Journal of Medicine* 2017;377(26):2597-2598.

¹⁷ Frank RG, Shahzad M, Feldman WB, Kesselheim AS. Biosimilar competition: early learning. NBER Working Paper No. 28460. Available at: <https://www.nber.org/papers/w28460>.

In the case of regulatory exclusivity, various laws provide different lengths of time for different categories of drugs. The 1984 Hatch-Waxman Act provided about 6-7 years of regulatory exclusivity for new brand-name drugs and 3 years for less innovative new formulations of already-existing drugs. The Orphan Drug Act of 1983 provided 7 years of regulatory exclusivity for drugs treating rare diseases. More recently, qualifying new antibiotics were provided an additional 5 years of regulatory exclusivity on top of their standard Hatch-Waxman exclusivity period from the Generating Antibiotic Incentives Now Act of 2012; new biologic drugs were provided 12 years of regulatory exclusivity in the Biologics Price Control and Innovation Act of 2010. Regulatory exclusivity starts at the date of drug approval, no matter how long a drug spent in pre-approval testing.

Patent exclusivity is determined by the issuance of patents. The basic requirements of a patent are that the invention must be new, useful, and not obvious. It must also be an advance over other existing products. Patents are issued by examiners at the US Patent and Trademark Office (USPTO) and currently last 20 years from the date they are filed. The patent on the active ingredient in a brand-name drug is usually filed around the time a drug is discovered or synthesized, and the time starts tolling at that point, which can be 5-10 years before it is FDA-approved, due to the time required for pre-clinical and clinical testing as well as FDA review. However, for key drug patents, US law grants pharmaceutical manufacturers an extension amounting to half the time spent in clinical trials and all the time spent in FDA review, up to 5 years. This is called “patent term restoration.” In a recent review led by Dr. Reed Beall in our group, we examined 170 top-selling drugs which had a first generic equivalent approved between 2000 and 2012 and found that about half (49%, or 83 drugs) received patent term restoration, with the median extension length being 2.75 years.¹⁸ Overall, drug patents subject to patent term restoration had a median exclusivity period after FDA approval of 13.75 years, compared with just 10 years for the patents covering the 87 drugs that did not receive patent term restoration.

Thus, regulatory and patent exclusivities covering brand-name drugs can run in parallel with each other, with regulatory exclusivity usually serving as a “floor” or minimum period of market exclusivity and patent exclusivity serving as the “ceiling” or outer limit of market exclusivity. They complement and supplement each other in preventing directly competing generics and biosimilars from reaching the market and lowering drug spending on a particular active ingredient used in medical care. Their intention is to encourage innovation, but as we will see, they can often have the opposite effect.

III. Strategies Brand-Name Manufacturers Use to Delay Generic or Biosimilar Entry

Patent and drug regulatory exclusivities were originally designed to provide an incentive and reward for investment in drug development by allowing investors and manufacturers to profit for a finite amount of time. But this system has become subject to many abuses. Because brand-name manufacturers sell their products at extremely high prices during the market exclusivity period and can expect to see the price fall once generic or biosimilar drugs reach the market, the length of the market exclusivity period is a critically important issue. As a result, brand-name manufacturers take numerous steps to try to extend the market exclusivity and delay generic or biosimilar entry as long as possible.

One of the most common and most effective strategies that manufacturers use to delay generic or biosimilar competition is by obtaining a thicket of additional patents, beyond the key patent on the underlying active ingredient. It has become common for manufacturers to seek dozens of patents—occasionally even hundreds—even for attributes that reflect no meaningful innovation or patient benefit. In addition to the underlying patent on the active ingredient, these additional patents can cover alternative drug formulations, crystalline structures, uses in treating various diseases, and methods of manufacturing.

¹⁸ Beall RF, Darrow JJ, Kesselheim AS. Patent term restoration for top-selling drugs in the USA. *Drug Discovery Today* 2019;24(1):20-25.

These are often called “secondary” patents because they cover features peripheral to the key active ingredient in a drug.¹⁹ In one review of 2 antiretroviral drugs approved to treat HIV, Tahir Amin and I found 2 base compound patents and 106 secondary patents covering compositions and formulations, intermediate compounds, polymorphs, prodrugs, manufacturing processes, methods of treatment, among others.²⁰ Since each patent lasts 20 years, and secondary patents are often sought after discovery of the initial product, a thicket of secondary patents can extend market exclusivity well past the expiration of the original market exclusivity; in the case of the HIV treatment that we looked at, the additional patents could have added 12 years to the market exclusivity period if they were allowed to remain in place. In a more recent study led by Dr. Beall, we also described a trend of more drugs being protected by “tertiary” patents, or patents that block generic or biosimilar entry but are yet a further step removed from secondary patents in that they do not even cover the drug itself, but rather cover the delivery mechanism of the drug, such as an injection tool, an inhaler, or a skin patch. The proportion of patents listed with the FDA that we classified as tertiary patents tripled from 3% (27/916) in 2000 to 9% (295/3,464) in 2016.²¹

A thicket of secondary and tertiary patents around a drug can block generic or biosimilar entry. In the case of inhalers used to treat lung disease, tertiary patents on the inhalers have prevented generic competition despite the fact that many of the active ingredients in the inhalers are decades old.²² The same principle applies to insulin products. In 2014, among the 19 patents listed with the FDA related to a group of insulin products, half covered just the injector delivery devices.²³ Patent thickets also make it possible for brand-name manufacturers to introduce new versions of their products to gain longer exclusivity with little or no clinical benefit for patients.²⁴ For example, in the case of the cancer drug imatinib (Gleevec), a new formulation of the active ingredient was introduced shortly after its FDA approval that was protected by secondary patents that extended its potential market exclusivity from July 2015 to November 2019 without offering meaningful additional clinical benefits.²⁵ In a study of drugs approved in 2002 led by Dr. Beall, we found that more than half were introduced in patentable new formulations in the subsequent 15 years, with many of these changes clinically trivial.²⁶ Manufacturers can extract substantial revenues from these trivial patented changes. In a recent study led by Dr. Rome of the multiple sclerosis drug glatiramer (Copaxone), we found that as the market exclusivity on the daily version was expiring the manufacturer introduced a version that could be taken 3 times per week instead of daily.²⁷ The company then used its marketing resources to persuade doctors to shift patients to the three-times-weekly version. This disrupted the market for the daily version and led to \$6.5 billion in additional drug expenditures that the US spent on the new

¹⁹ Kapczynski A, Park C, Sampat B. Polymorphs and prodrugs and salts (oh my!): an empirical analysis of “secondary” pharmaceutical patents. *PLoS One* 2012;7(12):e49470.

²⁰ Amin T, Kesselheim AS. Secondary patenting of branded pharmaceuticals: a case study of how patents on two HIV drugs could be extended for decades. *Health Affairs*. 2012;31(10):2286-2294.

²¹ Beall RF, Kesselheim AS. Tertiary patenting on drug-device combination products in the United States. *Nature Biotechnology* 2018;36(2):142-145.

²² Feldman WB, Gagne JJ, Kesselheim AS. Trends in Part D inhaler spending, 2012-2018. *Annals of the American Thoracic Society*. 2020 Nov 18. doi: 10.1513/AnnalsATS.202008-1082RL

²³ Luo J, Kesselheim AS. The evolution of insulin patents and market exclusivities in the USA, 2004-2014. *The Lancet Diabetes & Endocrinology* 2015;3(11):835-837.

²⁴ Amin T, Kesselheim AS. Secondary patenting of branded pharmaceuticals: a case study of how patents on two HIV drugs could be extended for decades. *Health Affairs*. 2012;31(10):2286-2294. doi:10.1377/hlthaff.2012.0107

²⁵ Chen CT and Kesselheim AS. The journey of generic imatinib: a case study in oncology drug pricing. *Journal of Oncology Practice* 2017;13(6):352-355

²⁶ Beall RF, Kesselheim AS, Sarpatwari A. New drug formulations and their respective generic entry dates. *Journal of Managed Care and Specialty Pharmacy* 2019;25(2):218-224.

²⁷ Rome BN, Tessema FA, Kesselheim AS. US spending associated with transition from daily to three-times-weekly glatiramer acetate. *JAMA Internal Medicine* 2020;180(9):1165-1172.

formulation instead of generics.²⁸ A federal appeals court ultimately held that the patents protecting the new version of glatiramer were invalid, but the additional spending had already occurred.

To deal with patent thickets protecting most brand-name drugs, current federal law relies on generic and biosimilar manufacturers to challenge these patents in court so that they may be found invalid or not infringed by the comparable generic or biosimilar formulation. These lawsuits show that many secondary and tertiary patents have been improperly granted because they lack novelty or only cover minor, obvious changes to the drug. The legal and scientific complexity of drug patent applications, combined with the heavy demands on patent assessors who are often not expert in the issues at stake, means that personnel in the US Patent and Trademark Office sometimes issue patents in error. By contrast, when patents cover real innovations—in the case of drugs, most commonly the primary patents on the underlying active ingredient—legal challenges are often far less successful. An analysis in *Science* revealed that legal challenges to active ingredient patents succeeded only 8% of the time, while challenges to secondary patents were successful 67% of the time.²⁹

But litigation over secondary and tertiary patents can take a long time and requires substantial resources; average litigation costs needed to overturn a patent grew to more than \$5 million in 2015.³⁰ In addition, in recent years, a large number of generic and biosimilar manufacturers have settled patent litigation cases with brand-name manufacturers, agreeing to keep the patents in place and not introduce their FDA-approved drugs onto the market in exchange for various financial benefits. This has been called “pay for delay” since in the 2000s and early 2010s, many of these settlements also involved cash transfers to the generic or biosimilar manufacturer.³¹ After a Supreme Court case in 2013 allowed such settlements to be challenged under the antitrust laws, direct payments as part of patent litigation settlements have become rare.³² Still, the delays caused by these settlements can be lengthy and problematic. In a study our group published in *Health Affairs* led by Dr. Dave, we reviewed 69 brand-name drugs that were predicted to lose market exclusivity between 2010-2016 and found that generic entry was delayed by more than one quarter for 31 products (45%), leading Medicaid to spend an estimated excess of \$761 million.³³ Thus, the delay in generic competition caused by patents that should never have been issued contributes to excess expenditures on brand-name drugs by public and private sector payors, and by patients. These patents also misdirect research by incentivizing firms to devise small tweaks to existing blockbusters.

Brand-name manufacturers also use other strategies to delay generic entry. For example, the Orphan Drug Act was passed in 1983 to encourage investment in research into treatments for rare diseases by providing 7 years of guaranteed exclusivity after drug approval in which the FDA cannot approve another version of the same active ingredient for the same indication. But this designation has sometimes been sought by manufacturers for drugs that were not new, that were used broadly off-label beyond the FDA-approved rare disease indication,³⁴ or that reached blockbuster sales despite the intent of the legislation to provide extra incentives for drugs for rare diseases that might not have been otherwise brought to

²⁸ *Id.*

²⁹ Hemphill CS and Sampat B. Drug patents at the Supreme Court. *Science* 2013;339:1386-1387.

³⁰ Darrow JJ, Beall RF, Kesselheim AS. The generic drug industry embraces a faster, cheaper pathway for challenging patents.

Applied Health Economics and Health Policy 2019;17(1):47-54.

³¹ Kesselheim AS, Murtagh L, Mello MM. “Pay-for-delay” settlements of disputes over pharmaceutical patents. *New England Journal of Medicine* 2011;365(15):1439-1445.

³² Carrier M. *FTC v Actavis: where we stand after 5 years*. IPWatchdog.com. June 18 2018. Available from:

<https://www.ipwatchdog.com/2018/06/18/ftc-v-actavis-stand-5-years/id=98536/>

³³ Dave C, Sinha MS, Beall RF, Kesselheim AS. Estimating the cost of delayed generic entry to Medicaid. *Health Affairs* 2020;39(6):1011-1017

³⁴ Kesselheim AS, Myers JA, Solomon DH, Winkelmayr WC, Levin R, Avorn J. The prevalence and cost of unapproved uses of top-selling orphan drugs. *PLoS One* 2012;7(2):e31894.

market.³⁵ In the case of the widely-used cholesterol-lowering medication rosuvastatin (Crestor), the manufacturer received approval in patients with a rare cholesterol-raising genetic mutation just two months before generics were poised to enter the market in July 2016 and then attempted to use this approval to delay generic entry.³⁶

Overall, a study led by Dr. Rome in our research group found that brand-name small molecule drugs receive an average of about 14.4 years of market exclusivity, while brand-name biologic drugs receive an average exclusivity period of 21.5 years.³⁷ One of those biologic products, adalimumab is a focus of today's hearing, so I will next provide some details of adalimumab's market exclusivity, which show how these strategies apply in this case.

IV. Application to Adalimumab (Humira)

Adalimumab (Humira) was the third tumor necrosis factor alpha (TNF α) blocker to reach the US market. The ability of this drug class to successfully treat chronic inflammatory diseases like rheumatoid arthritis and Crohn's disease was identified based on work in academic medical centers in places like University College London.³⁸ Work on adalimumab itself was initiated in 1993 through a collaboration including a German chemical company that sought its initial patents in 1994. Abbott (now Abbvie) bought the rights to the company and adalimumab in 2000 two years after the FDA approval of infliximab (Remicade) and etanercept (Enbrel), the first two TNF α inhibitors in the US, and it was approved by the FDA in late 2002 and initially launched in the US in 2003. It was initially marketed both in pen and pre-filled syringe forms and quickly became a top-selling product. Humira is currently the best-selling drug in the world, generating revenues for its manufacturer of \$20 billion in 2020.

The manufacturer sought and obtained numerous additional patents covering the product, its use, its manufacturing, and its delivery mechanisms. According to a report from the Institute for Medicines, Access and Knowledge (I-MAK), there have been 247 patent applications filed on adalimumab in the US, leading to 105 additional granted patents beyond the primary patent.³⁹ Interestingly, 89% of the total patent applications were filed after the drug's 2002 FDA approval and 49% after its first patent expired.⁴⁰ By comparison, just 76 patents were filed in Europe and 63 in Japan.⁴¹ While the primary patent on adalimumab was set to expire in 2016, this patent thicket threatened to extend market exclusivity to as long as 2037.⁴²

As 2016 approached, biosimilar manufacturers developed their own versions of adalimumab, and received tentative FDA approval based on demonstration of molecular similarity and comparable safety and efficacy. But before they could be widely sold in the US, biosimilar manufacturers had to navigate their way through the thicket of patents by engaging in litigation with Abbvie. For biosimilar manufacturer Amgen, for example, 61 patents were alleged to be infringed, 74 patents for biosimilar manufacturer Boehringer

³⁵ Sarpatwari A, Kesselheim AS. Reforming the Orphan Drug Act for the 21st century. *New England Journal of Medicine* 2019;381(2):106-108

³⁶ Pollack A. AstraZeneca pushes to protect Crestor from generic competition. June 27, 2016. *NY Times*. Available from: <https://www.nytimes.com/2016/06/28/business/astrazeneca-pushes-to-protect-crestor-from-generic-competition.html>.

³⁷ Rome BN, Lee CC, Kesselheim AS. Market exclusivity length for drugs with new generic or biosimilar competition, 2012-2018. *Clinical Pharmacology and Therapeutics* 2020 July 12 [epub before print].

³⁸ 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

³⁹ I-MAK. Humira. October 2020. Available from: <https://www.i-mak.org/wp-content/uploads/2020/10/i-mak.humira.report.3.final-REVISED-2020-10-06.pdf>.

⁴⁰ Id.

⁴¹ Id.

⁴² Id.

Ingelheim, and 84 for biosimilar manufacturer Sandoz. In settlements in 2017 and 2018, these biosimilar manufacturers agreed to remain off the US market until 2023, although they were allowed to sell their products in most countries in the European Union as soon as October 2018. In a study forthcoming in Clinical Pharmacology and Therapeutics led by Charlie Lee and Dr. Ameet Sarpatwari in our group, we estimated the cost of the delay of biosimilars of adalimumab after the expiration of the original patent, finding that Medicare alone could have saved about \$2.2 billion between 2016 and 2019.⁴³

In addition to setting up a thicket of secondary and tertiary patents, Abbvie worked to shift the market to a new formulation, a citrate-free version of Humira that was launched in May 2018. The citrate-free formulation is also lower volume. Abbvie claimed that the citrate-free version would cause less pain with the injections in direct-to-consumer advertising aimed at switching Humira users to the new formulation.⁴⁴ Abbvie set the price of the new version at the same rate as the original product, although we do not know whether Abbvie was offering differing rebates for the products to some payors. Since its introduction, citrate-free adalimumab has become increasingly popular, growing from about one-third of all adalimumab use in Medicaid in the first quarter of 2019 to 80% by the fourth quarter of 2020. In Medicare, the citrate-free adalimumab grew quickly to about 40% of use by 2019.

As a result of Abbvie's market exclusivity-extending strategies, in 2019, after 18.2 years on the market, adalimumab remains a mega-blockbuster product, accounting for over \$15 billion in US revenues. The pen delivery versions accounted for \$1.3 billion in Medicare Part D spending and its pre-filled syringe formulation accounted for \$357 million spending. The citrate-free formulation accounting for another \$896 million (after only 2.7 years on the market). All of these values are net spending and include estimated rebates obtained by Medicare Part D plans. Citrate-free adalimumab was also a major cost-driver for Medicaid, accounting for \$525 million in estimated net spending in 2019 alone, making it the third-highest net-spending drug in Medicaid. Biosimilar entry is expected in 2023, over 20 years after the product first reached the US market, but further delays may be possible.

V. Policy Solutions

There are a number of ways to protect and reward innovation fairly, yet ensure that there is timely entry of generic and biosimilar drugs after the end of a reasonable period of market exclusivity. Perhaps the most useful solution would be to ensure that low-quality patents are not granted by the USPTO in the first place or, if they are, that there is a more efficient pathway to overturn them before they become caught up in litigation and become the basis of brand/generic or brand/biosimilar settlements. One way to do that would be to allocate greater resources to the USPTO to ensure patent quality. As noted above, the European Patent Office (EPO) and Japan Patent Office (JPO) issued far fewer patents related to adalimumab than the USPTO did. In fact, studies show that the EPO and JPO issue fewer erroneous patents in general by spending more time and resources scrutinizing patents, retaining high-quality examiners, and having their employees work in teams.⁴⁵ In one study, a 50% increase in examination time was associated with a 10 percentage point decrease in invalid patents.⁴⁶ Under the Trump administration, the problem of bad patents worsened, as the USPTO issued directives that raised the bar for when an examiner could reject a patent, leading to a

⁴³ Lee CC, Najafzadeh M, Kesselheim AS, Sarpatwari A. Costs to Medicare of delayed adalimumab biosimilar availability. *Clinical Pharmacology and Therapeutics* 2021 [in press]

⁴⁴ <https://www.ispot.tv/ad/IuM7/humira-psoriasis-citrate-free>.

⁴⁵ Picard PM, Bruno VPDLP. Patent office governance and patent examination quality. *Journal of Public Economics* 2013;104:14-25; Chien CV. Comparative Patent Quality. *Arizona State Law Journal*; 2018; 50:71-140; Lemley MA, Sampat B. Examiner Characteristics and Patent Office Outcomes. *Review of Economics and Statistics* 2012;94:817-827; Lei Z, Brian DW. Why Weak Patents? Testing the Examiner Ignorance Hypothesis. *Journal of Public Economics* 2017;148:43-56.

⁴⁶ Frakes MD, Wasserman MF. Investing in ex ante regulation: evidence from pharmaceutical patent examination. Cambridge, MA: National Bureau of Economic Research; July 2020 (<https://www.nber.org/papers/w27579>).

25% decrease in related rejections.⁴⁷ The USPTO badly needs more resources; better agency regulation can give examiners more time, reflecting current practices in some patent offices around the world. Congress could also instruct the USPTO to develop new guidance relating to the patenting standards for drugs, to ensure that examiners have more authority to reject ineligible applications.⁴⁸ For example, if the USPTO were to apply a stricter interpretation of existing novelty and non-obviousness standards for drug patents, secondary and tertiary patents covering trivial modifications would be less likely to be granted while patents on truly novel and innovative drug products would remain available.⁴⁹

Another step would be to provide greater opportunity for administrative review of drug patents prior to litigation. In 2011, the America Invents Act set up the US Patent Trial and Appeals Board (PTAB) to weed out invalid patents to address “a growing sense that questionable patents are too easily obtained and are too difficult to challenge.”⁵⁰ The PTAB can review granted patents under a more reasonable evidentiary standard than is applied by the courts, and can entertain challenges from any interested party, not just generic or biosimilar manufacturers.⁵¹ The PTAB should be required to review all drug patents when they are listed with the FDA or are determined to be relevant to the biosimilar approval process.

A more far-reaching reform would be to allow brand-name drug or biologic manufacturers to only enforce one patent—the primary patent on the underlying active ingredient—for each drug approval or clinically meaningful change to an existing product.⁵² In this model, manufacturers could receive patent protection for innovative compounds, plus patent term restoration and the 6-month additional exclusivity that the US law provides to manufacturers that conduct FDA-requested tests of their drugs in children.⁵³ In a review of top-selling small-molecule drugs that lost market exclusivity from 2000-2012, we found that such a model would provide a median of 12.5 years of market exclusivity, but would also provide greater assurance of generic or biosimilar competition at the end of the period with greater efficiency and fewer resources required for litigation.⁵⁴ However, such a model would also need to account for patented innovations to existing products that offer clinical advantages to patients, and would need to be made compatible with the international Trade-Related Aspects of Intellectual Property Rights agreement.

Finally, in particularly onerous cases, the federal government can invoke an existing right under federal law to use patented products, seeking out alternative manufacturers for products made available through programs like Medicare and Medicaid provided it offers reasonable and entire compensation to the patent holder.⁵⁵ Although the government has refrained from using this authority in recent years when it was proposed to address pressing public health issues like HIV prophylaxis and treatments for hepatitis C

⁴⁷ Bloomfield D and Kesselheim AS. Biden can lower drug prices without Congress doing anything. *Washington Post* Jan 5 2021.

⁴⁸ *Id.*

⁴⁹ Vokinger KN, Kesselheim AS, Avorn J, Sarpatwari A. Strategies that delay market entry of generic drugs. *JAMA Internal Medicine* 2017;177(11):1665-1669.

⁵⁰ *MCM Portfolio LLC v. Hewlett-Packard Company*, No. 2015-1091 (Fed. Cir. Dec. 2, 2015).

⁵¹ Darrow JJ, Beall RF, Kesselheim AS. Will inter partes review speed US generic drug entry? *Nature Biotechnology* 2017;35(12):1139-1141.

⁵² See, e.g., Mukherjee S. Michael Bloomberg’s radical plan to cut prescription drug costs. *Fortune* January 26 2020. Available from: <https://fortune.com/2020/01/28/bloomberg-drug-pricing-patent-proposal/>; Feldman R. ‘One-and-done’ for new drugs could cut patent thickets and boost generic competition. *STAT First Opinion*. February 11, 2019, Available from: <https://www.statnews.com/2019/02/11/drug-patent-protection-one-done/>.

⁵³ Sinha MS, Najafzadeh M, Rajasingh EK, Love J, Kesselheim AS. Labeling changes and costs for clinical trials performed under the US Food and Drug Administration pediatric exclusivity extension, 2007 to 2012. *JAMA Internal Medicine* 2018;178(11):1458-1466.

⁵⁴ Beall RF, Darrow JJ, Kesselheim AS. A method for approximating future entry of generic drugs. *Value in Health* 2018;21(12):1382-1389.

⁵⁵ Kapczynski A and Kesselheim AS. Government ‘patent use’: a legal approach to reduce drug spending. *Health Affairs* 2016;35(5):791-797.

virus infection, it could also be applied in cases like adalimumab that remain protected by myriad secondary and tertiary patents for many years after their expected brand-name exclusivity period.

If steps cannot be taken to clear out the thickets of patents that threaten transition to an effective competitive market, then we might need to consider automatic price reductions for brand-name drugs after a reasonable period of time on the market;⁵⁶ one recent analysis of applying this concept to biologic drugs predicted potential cost-savings over the next 5 years of \$265 billion compared to the current model of biosimilar competition.⁵⁷ At the level of the pharmacy, we could allow closely similar drugs to be more easily substituted with each other by pharmacists even if they have patentable differences, if the FDA judges those drugs to be therapeutically interchangeable.⁵⁸ Such a move would broaden competitive markets and require manufacturers of slightly changed versions of a product to ensure that the modified product really offers important benefits to patients.

Finally, we can also take steps to ensure that manufacturers cannot use other statutory market exclusivity periods to improperly delay entry of generic or biosimilar drugs. For example, Orphan Drug Act designation for one rare disease should not be allowed to block generic or biosimilar versions of a drug to be used for other FDA-approved indications of the same active ingredient.⁵⁹ The 7-year exclusivity period offered for rare disease drugs could also be curtailed for initially qualifying drugs that end up being used in much larger populations after approval, or that bring in substantial revenue.⁶⁰ The 12-year regulatory exclusivity period provided for biologic drugs could also be shortened to a level concordant with small-molecule drugs, because biologic drugs do not spend longer time in drug development on average than small-molecule drugs.⁶¹

VI. Conclusion

Our current arrangements granting government-protected monopoly status to prescription drugs through exclusivity rights were designed to protect and reward innovation, but “gaming the system” can cause them to have the opposite effect. Such abuses can make it more lucrative for a drug company to fend off generic competitors for older products rather than to come up with important new discoveries that will benefit patients. This bloats health care costs and puts medication prices out of the reach of many patients. We need policy changes to ensure timely and efficient availability of generic and biosimilar competition after reasonable periods of market exclusivity; this will help contain our highest-in-the-world drug prices and actually improve meaningful drug innovation. In one review of pharmaceutical manufacturers with at least one FDA-approved product from 1985-2001, the most important predictor of new product introductions was the loss of exclusivity protection on a current product.⁶²

The prescription drug exclusivity system was intended to provide a reasonable, limited period after FDA approval during which brand-name manufacturers can earn fair, even generous revenues from their

⁵⁶ Dudzinski DM and Kesselheim AS. Scientific and legal viability of follow-on protein drugs. *New England Journal of Medicine* 2008;358:843-849.

⁵⁷ Bach PB and Trusheim MR. The drugs at the heart of our pricing crisis. *NY Times*. March 15 2021.

⁵⁸ Darrow JJ, Chong JE, Kesselheim AS. Reconsidering the scope of US state laws allowing pharmacist substitution of generic drugs. *BMJ* 2020;369:m2236.

⁵⁹ Walsh BS, Sarpatwari A, Rome BN, Kesselheim AS. Frequency of first generic drug approvals with “skinny labels” in the United States. *JAMA Internal Medicine* 2021 March 29 [epub ahead of print].

⁶⁰ Sarpatwari A, Kesselheim AS. Reforming the Orphan Drug Act for the 21st century. *New England Journal of Medicine* 2019;381(2):106-108

⁶¹ Beall RF, Hwang TJ, Kesselheim AS. Pre-market development times for biologic versus small-molecule drugs. *Nature Biotechnology* 2019;37(7):708-711.

⁶² Graham, Stuart J.H. and Higgins, Matthew John, *The Impact of Patenting on New Product Introductions in the Pharmaceutical Industry* (April 4, 2007). Available at SSRN: <https://ssrn.com/abstract=984628>.

products. Strategies used in the adalimumab and other similar cases upset this balance and impose undue costs on patients and the US health care system. There are several specific actions that Congress can take to ensure that generic and biosimilar competition can occur in a timely fashion while treating brand-name manufacturers fairly. These would have little detrimental effect on meaningful drug innovation, but would reduce overall health care spending in the US, make medications more affordable, and promote improved patient outcomes.