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2018 Stuart Rome Lecture: Origins of and Potential Solutions to High Prescription Drug Prices in the U.S.

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2018 STUART ROME LECTURE: ORIGINS OF AND POTENTIAL SOLUTIONS TO HIGH PRESCRIPTION DRUG PRICES IN THE U.S.

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I. INTRODUCTION

Prescription drug prices are one of the fastest rising health care costs, becoming an increasing burden for patients and our health care system. The essential policy dilemma is that while drugs are among the most cost-effective interventions in medicine and the drug industry plays an important role in bringing these products forward—a process that can require substantial resources—increasing drug prices in the U.S. can make important breakthroughs unaffordable to many of our patients. Since high drug prices can lead to poor clinical consequences and have become a major driver in U.S. health care spending, this review is intended to provide an overall landscape of U.S. prescription drug spending, to address widely discussed explanations for high drug prices, and finally to review some proposed interventions and policy solutions.

II. BACKGROUND

Prescription drug spending in the U.S. rose 12% in 2015 and another 6% in 2016.[1] Total drug spending in 2016 was $450 billion, which accounted for about 22% of health care spending, 19% of Medicare spending, and 19% of employer-based insurance benefits.[2] Some health insurance companies have reported that

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1. IQVIA INST. FOR HUMAN DATA SCI., MEDICINES USE AND SPENDING IN THE U.S.: A REVIEW OF 2016 AND OUTLOOK TO 2021 6 (2017).

2. *See* IQVIA INST. FOR HUMAN DATA SCI., MEDICINES USE AND SPENDING IN THE U.S.: A REVIEW OF 2016 AND OUTLOOK TO 2021 6 (2017); https://www.iqvia.com/institute/reports/medicines-use-and-spending-in-the-us-a-review-of-2016 (describing total drug and health care spending in the United States);

drugs now account for one of every four dollars they spend on health care.[3] U.S. drug prices and spending far exceed those of other similar industrialized countries around the world. For example, countries like Canada, Germany, France, and Australia, all of which have excellent health care systems, on average spend about $400 per capita compared to the $850 the U.S. spends per capita on prescription drugs.[4] The main driver of prescription drug spending is brand-name drugs, which make up only about 10% of prescriptions but three-quarters of drug spending.[5] Prescription drug prices overall have been increasing substantially over the last decade. There was a 208% increase in prices of the most commonly used brand-name drugs from 2008 to 2016, a 12% increase in the Consumer Price Index, and a 28% increase in aggregate health care spending.[6]

This is not a new phenomenon, as one study found that brand-name cancer drug launch prices have been rising exponentially over the last 50 years.[7] But in recent years, we have seen that increases in drug prices are also not limited to brand-name products. In 2015, Turing Pharmaceuticals raised the price of pyrimethamine (Daraprim), a decades-old drug for patients with an infection that can sometimes arise among patients with reduced immune systems such as end-stage HIV infection, from $13.50 to $750 a pill.[8] Overall, generic drugs are still extremely inexpensive and among the most economical products in the U.S.

MEDICARE PAYMENT ADVISORY COMM'N, REPORT TO THE CONGRESS: MEDICARE AND THE HEALTH CARE DELIVERY SYSTEM 109 (2016), http://www.medpac.gov/docs/default-source/reports/june-2016-report-to-the-congress-medicare-and-the-health-care-delivery-system.pdf?sfvrsn=0 (describing breakdown of Medicare spending in the U.S.); *see also* Drew Altman, *Prescription Drugs' Sizable Share of Health Spending*, HENRY J. KAISER FAMILY FOUNDATION (Dec. 13, 2015), https://www.kff.org/health-costs/perspective/prescription-drugs-sizable-share-of-health-spending/; Drew Altman, *Prescription Drugs' Sizable Share of Health Spending*, WALL ST. J. (Dec. 13, 2015), https://blogs.wsj.com/washwire/2015/12/13/prescription-drugs-sizable-share-of-health-spending/ (explaining health care spending for employer-based insurance benefits).

3. Michael Sherman et al., *Prescription Medicines Account for One in Four Dollars Spent by a Commercial Health Plan*, HEALTH AFF. BLOG (Aug. 24 2018), https://www.healthaffairs.org/do/10.1377/hblog20180821.820628/full/.

4. Aaron S. Kesselheim et al., *The High Cost of Prescription Drugs in the United States: Origins and Prospects for Reform*, 316 JAMA 858, 859 (2016).

5. *Id.* at 860.

6. EXPRESS SCRIPTS, 2016 DRUG TREND REPORT 31 (2017) (providing a graph that depicts the 208% increase); Aaron S. Kesselheim, et al., *The High Cost of Prescription Drugs in the United States: Origins and Prospects for Reform*, 316 JAMA 858, 860 (2016) (describing a nationwide hike in the price index of prescription medications).

7. Peter B. Bach, *Monthly and Median Costs of Cancer Drugs at the Time of FDA Approval, 1965-2015*, MEMORIAL SLOAN KETTERING CANCER CENT., https://www.mskcc.org/research-programs/health-policy-outcomes/cost-drugs (last visited Nov. 9, 2018).

8. Andrew Pollack, *Drug Goes From $13.50 a Tablet to $750, Overnight*, N.Y. TIMES (Sept. 20, 2015), https://www.nytimes.com/2015/09/21/business/a-huge-overnight-increase-in-a-drugs-price-raises-protests.html.

health care system. However, there are parts of the generic market that do not work efficiently, leading to price hikes.

The clinical consequences of increasing drug prices are well-documented. Studies have found that patients who were prescribed a costly brand name product rather than a more affordable generic alternative adhered less well to treatment and, as a result, had worse health outcomes.[9,10] High prices are directly felt by the millions of patients without prescription drug insurance, as well as by patients with insurance via out-of-pocket costs. With rising prices leading to increased insurance premiums, some insurers have implemented cost-containment strategies that have transferred more drug expenses onto patients' shoulders through deductibles and co-payments.[11] Medicaid programs, which do not charge co-payments or substantial cost-sharing, have had to cut back on other services and tighten eligibility requirements due to expanding prescription drug budgets.[12] According to a survey in 2016, about one in every five patients reported that they, or another family member did not fill a prescription in the last year due to costs.[13]

III. EXPLANATIONS FOR HIGH DRUG PRICES

Many reasons have been offered for why prescription drug prices have risen so substantially in recent years. Some contend that these high prices are connected to innovation in the field. Naturally, since brand-name drug companies are involved in the development and testing of the investigational drugs that are submitted to the Food and Drug Administration (FDA), approved, and then marketed, they play a major role in the innovation pathway and receive much of the revenue that comes from these high prices. However, it is also important to recognize the limitations of the claims that link high drug prices to innovation. Many of the most transformative drugs that have come through in the past few decades originated in publicly funded research, supported by the National Institutes of Health and performed in academic medical centers.[14] This

9. William H. Shrank et al., *The Implications of Choice: Prescribing Generic or Preferred Pharmaceuticals Improves Medication Adherence for Chronic Conditions*, 166 *ARCH INTERN MED. 332, 332–35 (2006).*

10. Joshua J. Gagne et al., *Comparative Effectiveness of Generic and Brand-Name Statins on Patient Outcomes: A Cohort Study*, 161 ANN INTERN MED. 400, 405 (2014).

11. Amy Kapczynski & Aaron S. Kesselheim, *'Government Patent Use': A Legal Approach to Reducing Drug Spending*, 35 HEALTH AFF. 791, 791–93 (2016).

12. Aaron S. Kesselheim et al., *The High Cost of Prescription Drugs in the United States Origins and Prospects for Reform*, 316 JAMA 858, 864 (2016).

13. THE HENRY J. KAISER FAMILY FOUND., KAISER HEALTH TRACKING POLL: HEALTH CARE PRIORITIES FOR 2017 22 (2016), http://files.kff.org/attachment/Topline-Kaiser-Health-TrackingPoll-Health-Care-Priorities-for-2017.

14. Aaron Kesselheim et al., *The Roles of Academia, Rare Diseases, and Repurposing in the Development of the Most Transformative Drugs*, 34 HEALTH AFF. 286, 287, 291 (2015).

work makes drug identification possible by uncovering the key science and translational discoveries that make drug identification possible. In some cases, scientists have been integrally involved in developing the products themselves; developing monoclonal antibodies or taking drug samples through a proof of concept testing before drug manufacturers get involved as a partner to help finance and organize later-stage clinical trials. Large drug manufacturers spend about 13 to 20% of their revenues on research and development.[15] By contrast, they spend 31% on sales, marketing and administration.[16] One review estimated that much of the direct investment in research by large drug manufacturers is directed towards already-approved products, with approximately 2.2% being invested in research that could lead to future transformative discoveries.[17]

Another common justification for high drug prices is that they derive from high pre-approval clinical testing requirements. However, over the past few decades, it has been increasingly easier to meet the FDA standards of efficacy and safety for new drug approval. In the recent decade, about a third of all new drugs are approved on the basis of a single pivotal trial. Two-thirds of drugs are approved based on data from pivotal trials lasting six months or shorter, even if the drugs are chronic disease medications intended to be taken by patients for much longer.[18] Half of all drugs are approved based on effects observed in surrogate measures as opposed to actual clinical endpoints.[19] Surrogate measures are laboratory tests or other physical measurements that are easier to measure and often occur before a clinical event may be expected. Drugs approved in recent years are tested on average in fewer than one thousand patients in their pivotal clinical trials.[20]

Furthermore, the FDA has a number of expedited development or approval pathways for drugs that are particularly important, meet an unmet medical need, or treat a serious or life-threatening condition. For example, drugs given a Priority Review designation must be reviewed within six months, as compared to the standard ten-month review period. In 2012, the Breakthrough Therapy designation was created to move drugs through pre-approval testing as quickly as possible. In recent years, about three-quarters of all newly approved drugs

15. Jerry Avorn, POWERFUL MEDICINES: THE BENEFITS, RISKS, & COSTS OF PRESCRIPTION DRUGS 205 (Alfred A. Knopf ed., 2004).

16. *Id.*; Aaron S. Kesselheim, et al., *The High Cost of Prescription Drugs in the United States: Origins and Prospects for Reform*, 316 JAMA, 858, 863 (2016).

17. Donald W. Light & Joel Lexchin, *Foreign Free Riders and the High Price of US Medicines*. 331 BMJ 958, 959 (2005).

18. Nicholas S. Downing, et. al., *Clinical Trial Evidence Supporting FDA Approval of Novel Therapeutic Agents, 2005-2012*, 311 JAMA, 368, 369–72 (2015).

19. *Id.*

20. *Id.*

qualified for one or more of these special pathways.[21] Studies have found that drugs in these pathways on average offer more quality-adjusted life years (QALYs) than non-expedited drugs.[22] However, it is also the case that less-innovative second- and later-line drugs in a class are qualifying for one of these pathways.[23]

These trends have made the FDA the fastest regulatory agency in the world in terms of new drug approvals. The FDA's new oncology drug approval review times were found on average to be shorter than European Medicines Agency review times. Novel therapeutics are now more likely to be approved in the U.S. before being marketed in Europe or Canada.[24] In recent years, nearly all approved drugs are now being approved on the first cycle of review, illustrating the FDA's modern-day efficiency.[25]

Are drugs expensive simply because they impart good clinical value? The Institute for Clinical and Economic Review (ICER) regularly conducts formal value-based assessments of drugs, evaluates how effectively the drugs work, and what the prices of alternative products are in order to determine whether the drug is priced at a level that is reasonably consistent with its value.[26] ICER's assessments have shown that while some expensive drugs are priced in line with value, many are priced at levels much greater than their estimated value.[27]

The underlying reason for high drug prices is the U.S. allows pharmaceutical manufacturers to charge whatever the market will bear. Indeed, rather than being driven by innovation or FDA requirements, many pharmaceutical manufacturers admit that prices are set based on what others are setting; a commonly stated justification for high prices is that the prices of their

21. Jonathan J. Darrow et al., *The FDA Breakthrough-Drug Designation- Four Years of Experience*, 378 NEW ENG. J. MED. 1444, 1445 (2018).

22. James D. Chambers et al., *Drugs Cleared Through the FDA's Expedited Review Offer Greater Gains Than Drugs Approved by Conventional Process*, 36 HEALTH AFF. 1408, 1408–14 (2017).

23. Aaron Kesselheim et al., *Trends in Utilization of FDA Expedited Drug Development and Approval Programs, 1987-2014: Cohort Study*, BMJ, Aug. 17, 2015, at 5.

24. Nicholas S. Downing et al., *Regulatory Review of Novel Therapeutics—Comparison of Three Regulatory Agencies*, 366 NEW ENG. J. MED. 2284, 2290–91 (2012).

25. John K. Jenkins, Director, Office of New Drugs, Center for Drug Evaluation and Research, CDER New Drug Review: 2015 Update at the FDA/CMS Summit (Dec. 14, 2015), https://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/UCM477020.pdf.

26. *See generally*, INST. FOR CLINICAL AND ECON. REV., https://icer-review.org/about/ (last visited Nov. 9, 2018).

27. *Id.*; Peter B. Bach & Steven D. Pearson, *Payer & Policy Maker Steps to Support Value–Based Pricing for Drugs*, 314 JAMA 2503, (2015) (discussing a review by ICER of 2 inhibitor drugs for high cholesterol showing that a reasonable value–based price range of the long–term clinical benefits would be lower than the annual price list).

drugs are in line with other therapies or treatments.[28] Exacerbating this problem are strategies that undercut competition and hinder payors' abilities to provide counterweights that might reduce high prices; that is, the market will bear excessive prices well out of proportion to the value that new drugs provide because it is highly inefficient. In the next section, I will review how changes to make competition more effective are among the most promising strategies for bringing prices down to more reasonable levels.

IV. ADDRESSING HIGH DRUG PRICES IN THE U.S. MARKET

Addressing inappropriately high drug prices requires different approaches to each segment of a drug's development course. After the pre-approval period—since drug prices are not strongly associated with the cost of drug development—the next three major time segments are the brand-name market exclusivity period, the transition to generic competition, and the multisource market. Interventions in these areas may affect drug prices, and I will review them in turn.

A. Brand-Name Market Exclusivity Period

When the FDA approves a new drug, the law guarantees at least about six to seven years of market exclusivity, during which time the FDA will not approve any direct competitors, allowing manufacturers to establish prices.[29] There are some variations to the length of market exclusivity depending on the product type. For example, certain antibiotics get an additional 5 years, and biologics get twelve years.[30] In addition to this guaranteed minimum period of market exclusivity, brand-name drugs are protected by patents that last twenty years.[31] The first patent on the underlying active ingredient is obtained around the time the active ingredient is synthesized or discovered, and therefore a certain amount of time remaining on it has usually expired by the time the drug reaches the market. (This time is offset by patent term restoration that adds back to the patent

28. Aimee Picchi, *The Cost of Biogen's New Drug: $750,000 Per Patient*, CBS NEWS MONEYWATCH (Dec. 29, 2009, 2:00 PM), https://www.cbsnews.com/news/the-cost-of-biogens-new-drug-spinraza-750000-per-patient/ (noting that a pharmaceutical company claimed that a $750,000 price tag on a rare disease drug is consistent with other therapies for rare diseases); Courtney Hutchison, *Provenge Cancer Vaccine: Can You Put a Price on Delaying Death?*, ABC NEWS (July 29, 2010), https://abcnews.go.com/Health/ProstateCancerNews/provenge-cancer-vaccine-months-life-worth-100k/story?id=11269159; Judy Silber, *Onyx Gets OK for Kidney Cancer Drug*, CONTRA COSTA TIMES, Dec. 21, 2005, at F4; Amy Dockser Marcus, *Price Becomes Factor in Cancer Treatment*, WALL ST. J., Sept. 7, 2004, at D.1.

29. 21 C.F.R. § 314.108 (2016).

30. 21 U.S.C. § 355f(a) (2012); 42 U.S.C. § 262(k)(7)(A) (2010).

31. 35 U.S.C. § 154(a)(2) (2015).

the time of FDA review and half the time of clinical development.)[32] One study found that on average new drugs get about 12 to 14 years of competition-free exclusivity, while first-in-class drugs—often the most innovative products—get on average about 14 to 15 years.[33]

During the market exclusivity period, there are important limits placed on public and private payors that prevent them from negotiating effectively with manufacturers. For example, Medicare, the government insurance program for patients over age 65, covers about 45 million people and accounts for about a third of the nation's drug expenditure, but it does not use a national formulary or negotiate drug prices on behalf of the individual Medicare Part D plans that provide outpatient drug benefits to enrollees.[34] There are also six protected drug classes for which Medicare Part D plans have to cover all approved drugs, such as drugs for cancer and mental illness. Although Part D plans can use formulary management tools such as prior authorization, this rule undermines effective price negotiation, since it is hard to negotiate an effective price if a Part D insurer is forced by the federal govt to cover the drug, even if it is no better than one or two or three similar products. Similarly, Medicaid, the federal- and state-based insurance program for poor patients that covers about 75 million people, cannot exclude most FDA-approved drugs from its formulary (it, too, can use formulary management tools).[35] As a result, while Medicaid is guaranteed a certain best price based on what the drugs are sold for in the private market, states are often unable to negotiate additional savings. Among the federal government payors, the Department of Veterans Affairs (VA) has the most flexibility in terms of setting its formulary and in negotiating on behalf of all its enrollees around the country. As a result, the VA often pays far less for many drugs.

Private payors also have limitations on their abilities to negotiate prices. One of the primary limitations is the lack of comparative effectiveness information at the time of approval, which documents how effectively drugs work compared to other drug or non-drug treatments on the market. In a sample of 197 drugs approved in years 2000-2010, only half of the drugs had comparative effectiveness information at the time of approval.[36] Comparative effectiveness information does not reliably emerge after approval either, since there is no system for reliably generating such evidence. Formulary management

32. 35 U.S.C. §156(c) (2012).

33. Bo Wang et al., *Research Letter: Variation in Time of Market Exclusivity among Top-Selling Prescription Drugs in the United States*, 175 JAMA 635, 636 (2015).

34. Aaron S. Kesselheim et al., *The High Cost of Prescription Drugs in the United States: Origins and Prospects for Reform*, 316 JAMA 858, 862 (2016).

35. *Id*.

36. Nikolas H. Goldberg et al., *Availability of Comparative Efficacy Data at the Time of Drug Approval in the United States*, 305 JAMA 1786, 1787 (2011).

tools used by private insurers can also be undermined by manufacturers; for example, as part of their promotional outreach, manufacturers have offered coupons to patients that counteract increased cost-sharing levels or provided physician offices with strategies to circumvent prior authorization paperwork. In addition, some state laws require private payors to cover drugs, making it difficult for payors to negotiate a reasonable price. For example, the National Conference of State Legislatures conducted a study reviewing state laws and found that about two-thirds of states required private payors to cover off-label uses of cancer drugs.[37]

Possible solutions for improving competitive price negotiation during the market exclusivity period include giving public payors greater latitude to use formularies or tools like therapeutic substitution, which would allow these payors to more efficiently direct patients to equally effective therapies that may cost less. When implemented in an evidence-based and transparent way, formulary tools may be useful in helping to provide greater leverage in the negotiating process with the manufacturer. Authorizing Medicare to negotiate prices for drugs has been widely suggested as an alternative solution that could be accomplished by changing a specific part of the Medicare Part D statute. However, economists have found that authorizing Medicare to negotiate drug prices will likely lead to small savings without broader formulary oversight, which can be included as part of that legislative change.[38]

In the private market, accountable care organizations are starting to emerge that provide the opportunity to pair health services and drug costs; this allows physicians to benefit from prescribing drugs optimally rather than from prescribing expensive drugs that do not add value. Producing and actively disseminating information about the clinical and economic value of drugs would be helpful for individuals who are working on negotiating with private manufacturers and payors. The Patient-Centered Outcomes Research Institute, created in 2010, was originally conceived to conduct this value-based research on drugs. However, the political process diverted it away from funding the kind of comparative effectiveness research that would help private payors make decisions in the pharmaceutical industry.[39] Local interventions can include

37. *See* Karmen Hanson & Erik Bondurant, CANCER INSURANCE MANDATES AND EXCEPTIONS, (Nat'l Conf. of St. Legis. eds., 2009) (stating the states that have off-label drug use as a cancer-related benefit and offering).

38. *See* Juliette Cubanski & Tricia Neuman, *Searching for Savings in Medicare Drug Price Negotiations*, KAISER FAMILY FOUNDATION 1, 3 (2018), http://files.kff.org/attachment/issue-brief-searching-for-savings-in-medicare-drug-price-negotiations.

39. *See* Aaron S. Kesselheim et al., *The High Cost of Prescription Drugs in the United States: Origins and Prospect for Reform*, 316 JAMA 858, 866 (2016) (stating that Congress precluded Patient-Centered Outcome Research Institute from considering drug prices, instead the Patient-Centered Outcome Research Institute focused on patient engagement and decision aids).

integrating value-based prescribing into physicians' professional education, setting up electronic medical record point-of-care reminders,[40] or enhanced institution-level decision-making. For example, Memorial Sloan Kettering Cancer Center determined that the drug ziv-aflibercept was not cost-effective and decided not to use it at its institution, resulting in the manufacturer giving the Center a particularly high discount on the product to keep it on the institution's formulary.[41]

B. Brand-to-Generic Transition

The next period in the drug life cycle is the brand-to-generic transition period. The only type of competition that consistently and substantially lowers prescription drug prices comes from interchangeable generic drugs that emerge after the market exclusivity period ends. State drug product selection laws then facilitate the process of circulating generic drugs to patients by mandating or authorizing pharmacists to fill a prescription with a generic drug. This can occur even when a physician writes for a brand-name drug. Automatic substitution helps generic manufacturers compete based on price and ensures that prices reach closer to the cost of production.

However, this brand-to-generic transition period can be delayed or prolonged. For example, the government provides an additional six months of exclusivity if a manufacturer tests its drug with children.[42] This incentive derives its value from delaying generic entry. In addition, nearly all manufacturers seek, and the federal government grants, dozens of additional patents on their drugs during the course of development and the brand-name exclusivity period.[43] Generic manufacturers must then sue to invalidate these patents before bringing their drugs to market. Such secondary patents cover peripheral components of the drug as well as different compositions, formulations, polymorphs, and prodrugs, which have the potential to extend market exclusivity of these drugs by years.[44] These patents also facilitate product hopping, in which the brand-

40. *Id*. at 866–67.

41. *See* Peter B. Bach et al., *In Cancer Care, Cost Matters*, N.Y. TIMES (Oct. 14, 2012), https://www.nytimes.com/2012/10/15/opinion/a-hospital-says-no-to-an-11000-a-month-cancer-drug.html (explaining Sloan-Kettering's decision to stop prescribing Zaltrap in favor for a less expensive and equally effective drug from the perspective of the prescribers); *see also Ziv-Aflibercept*, NAT'L CANCER INST., https://www.cancer.gov/about-cancer/treatment/drugs/ziv-aflibercept (last updated Mar. 9, 2018) (indicating that Zaltrap is the brand name for ziv-aflibercept).

42. *Qualifying for Pediatric Exclusivity Under Section 505A of the Federal Food, Drug, and Cosmetic Act: Frequently Asked Questions on Pediatric Exclusivity (505A), FDA, https://www.fda.gov/Drugs/DevelopmentApprovalProcess/ucm077915.htm (last updated Nov. 30, 2016).*

43. Kerstin N. Vokinger et al., *Strategies That Delay Market Entry of Generic Drugs*, 177 JAMA INTERNAL MED. 1665, 1665–66 (2017).

44. Tahir Amin & Aaron S. Kesselheim, *Secondary Patenting of Branded Pharmaceuticals: A Case Study*

name manufacturer markets additional products and "hops" their patients over to those products. For example, seven years after the FDA approved memantine in 2003 for Alzheimer's disease, it approved an extended-release version of memantine.[45] Then, in 2015, Forest launched the extended-release once-a-day version to replace the original twice-a-day formulation, announcing also that it was going to remove the twice-a-day version from the market.[46] If the removal occurred before the generic was introduced, it would have required every patient to switch over, undermining the market for the soon-to-be-introduced generic. This attempt at product hopping was blocked by a lawsuit from the New York Attorney General.[47] Patent litigation can also lead to settlements in which the generic manufacturer agrees to drop the lawsuit in exchange for some valuable consideration from the brand-name manufacturer. While settlements can be efficient ways to end litigation, these settlements also prop up weak patents and delay generic entry.

Other strategies intended to delay generic entry do not directly involve patents. For example, to garner FDA approval of its a generic drug, a manufacturer needs to conduct bioequivalent studies showing that its product is equivalent to the brand-name version. Yet there have reportedly been over 150 cases in which brand-name manufacturers have refused to provide samples to generic manufacturers for such bioequivalence testing.[48] Another delaying strategy including filing citizen petitions with the FDA.[49] Most citizen petitions related to generic drugs are filed by brand-name manufacturers claiming that their product has a special characteristic, and thus, the generic should not be approved, which can have the effect of delaying entry of a generic.[50] The manufacturer for the brand-name oral antibiotic Vancocin filed 24 different citizen petitions over a period of six years.[51]

of How Patents on Two HIV Drugs Could Be Extended for Decades, 31 HEALTH AFF. 2286, 2291 (2012).

45. Vincent C. Capati & Aaron S. Kesselheim, *Drug Product Life-Cycle Management as Anticompetitive Behavior: The Case of Memantine*, 22 J. MANAGED CARE & SPECIALTY PHARMACY 339, 339–40 (2016).

46. Vincent C. Capati & Aaron S. Kesselheim, *Drug Product Life-Cycle Management as Anticompetitive Behavior: The Case of Memantine*, 22 J. MANAGED CARE & SPECIALTY PHARMACY 339, 339–40 (2016).

47. State of New York v. Actavis, 787 F.3d 638, 663 (2015).

48. Kerstin N. Vokinger, et al., *Strategies That Delay Market Entry of Generic Drugs*, 177 JAMA INTERNAL MED. 1665, 1666 (2017).

49. *See* Michael A. Carrier & Carl Minniti, *Citizen Petitions: Long, Late-Filed, and At-Last Denied*, 66 AM. UNIV. L. REV. 305, 305–06 (2016) (analyzing 505(q) citizen petitions filed with FDA as a form of under-recognized anticompetitive behavior and concluding that 92% are filed by brand-name pharmaceutical companies with indicia of their purpose being to delay generic approval).

50. Kerstin N. Vokinger et al., *Strategies that Delay Market Entry of Generic Drugs*, 177 JAMA INTERNAL MED. 1665, 1667 (2017).

51. *Id.; see also FTC Charges that Shire ViroPharma Inc. Abused Government Processes through Serial,*

A possible solution that could help with cutting through the thicket of patents in an economically efficient way is re-examination of patents by the Patent Trial and Appeals Board, which was created in 2011 to administratively review patents that had been approved by the Patent and Trademark Office.[52] Others ideas include reconsideration of the appropriateness of brand to generic settlements and passage of CREATES Act, which would make it illegal for brand-name manufacturers to withhold samples for their products when generic manufacturers request them.[53]

C. Multisource period

The final period of a drug's development course is the multi-source generic competition period. During this period, the price that a drug achieves is a function of the amount of competition that exists in the market; that is, simply because a drug is generic does not necessarily mean that it is inexpensive. The price of a generic drug depends on the number of competitors that can drive its price down. One study reviewed the average relative price per dose of a drug based on the number of manufacturers that were on the market and found that if there is only one generic manufacturer, the price of the generic version was 87% of the brand-name version.[54] With two generic manufacturers, the price of the generic was 77% of the brand name's price, three manufacturers, 60%, and starting when there are four or more manufacturers on the market, the relative prices of the generic to the brand-name were 50% or lower. [55]

However, some drugs may not have sufficient generic competition to keep the price down to what might be expected. Our 2016 review of a sample of drugs that had been approved in the past 25 years and lacked market exclusivity found that 15% of the drugs had no generic competitors and about a third of them had three or fewer generic competitors on the market, putting them at risk of

Sham Petitioning to Delay Generics and Maintain its Monopoly over Vancocin HCL Capsules, FTC (Feb. 7, 2017), https://www.ftc.gov/news-events/press-releases/2017/02/ftc-charges-shire-viropharma-inc-abused-government-processes (announcing the filing of a complaint against the manufacturer, alleging antitrust violations including abusing the citizen petition process in order to delay generic Vancocin entry to the market).

52. Jonathan J. Darrow et al., *The Generic Drug Industry Embraces a Faster, Cheaper Pathway for Challenging Patents*, APPLIED HEALTH ECON. & HEALTH POL'Y, Aug. 2018, at 1–2.

53. S. 974, 115th Cong. (2017).

54. Chintan V. Dave et al., *Prices of Generic Drugs Associated with Numbers of Manufacturers*, 377 N. ENGL. J. MED. 2597, 2597–98 (2017).

55. *Id.* at 2597–98. (extrapolating from the data that with each additional manufacturer, the relative prices decreased at a slower rate).

shortages, high prices, and acquisition by pharmaceutical entrepreneurs.[56] Importation of generics from other well-regulated markets could be a possible intervention to respond to the lack of a vibrant generic drug market in these cases.[57] In a sample of U.S. drugs that had insufficient competition, about two-thirds of them were being produced by at least one other independent manufacturer in one or more foreign markets.[58] Since there is ample evidence suggesting that drug supplies in other countries are safe, the FDA recently announced that it was forming a task force to examine this approach.[59]

Ensuring effective generic competition requires sufficient funding of the FDA's Office of Generic Drugs. The office was historically underfunded, leading to long delays in generic approval times until 2012, when Congress authorized manufacturer user fees to support generic drug applications. Since then, the FDA has approved new generics much more quickly and has been able to review the existing backlog of applications.[60] Additionally, the FDA has recently announced that it will begin to expedite the review of generic applications to address a lack of effective competition.[61] Greater funding can also support the science of generic drug production to ensure that even complex products have interchangeable versions available.

V. CONCLUSIONS

One of the common misperceptions about the drug pricing controversies in the U.S. is that better pricing mechanisms will undercut innovation. As discussed previously, publicly funded research has helped produce many of our most

56. *See* Ravi Gupta et al., *Generic Drug Approvals Since the 1984 Hatch-Waxman Act*, 176 JAMA INTERNAL MED., 1391 1391–93 (Sept. 2016) (referencing the table on page 1392, explaining how 15% of drugs had no generic competitors and 1/3 had three of fewer generic competitors on the market).

57. *See* Michael Fralick et al., *The Price of Crossing the Border for Medications*, 377 NEW ENG. J. MED. 311, 311–13 (2017) (highlighting past examples and benefits of drug importation into the United States).

58. *See* Thomas J. Bollyky & Aaron S. Kesselheim, *Can Drug Importation Address High Generic Drug Prices?* 15 tbl.1 (Hutchins Ctr., Working Paper No. 29, 2017), https://www.brookings.edu/wp-content/uploads/2017/05/wp29_bollykykesselheim_drugimportation.pdf (finding 69 U.S drugs with insufficient generic competition, of which 44 were made by at least one different manufacturer approved outside the U.S.).

59. *See* FDA, STATEMENT FROM FDA COMMISSIONER SCOTT GOTTLIEB, M.D. ON NEW STEPS TO FACILITATE EFFICIENT GENERIC DRUG REVIEW TO ENHANCE COMPETITION, PROMOTE ACCESS AND LOWER DRUG PRICES (2018), https://www.fda.gov/NewsEvents/Newsroom/%20PressAnnouncements/ucm591184.htm. (explaining the plan to improve the efficiency and predictability of the FDA's generic review process).

60. *Id.* at 8.

61. *See* FDA, STATEMENT FROM FDA COMMISSIONER SCOTT GOTTLIEB, M.D. ON NEW STEPS TO FACILITATE EFFICIENT GENERIC DRUG REVIEW TO ENHANCE COMPETITION, PROMOTE ACCESS AND LOWER DRUG PRICES (2018), https://www.fda.gov/NewsEvents/Newsroom/%20PressAnnouncements/ucm591184.htm. (explaining the plan to improve the efficiency and predictability of the FDA's generic review process).

transformative new drugs, so as long as these funds are maintained, there will always be sufficient new targets and pathways for later-stage investment. Second, the recommendations listed above are intended to bring US drug prices in line with clinical value—that is, to rationalize payment for drugs in the US so that US patients stop paying exorbitant prices for drugs that offer minimal clinical impact. Paying for drugs based on their value may mean that there are some circumstances in which prices will be very high for drugs that offer substantial gains over existing treatments. But Medicare, Medicaid and other US payors will be able to better afford to cover such products for the patients who need them by not wasting vast sums on drugs that do not offer such advantages. By contrast, in the existing marketplace, incentives for innovation are misaligned with patient or public health goals because even marginally effective drugs or incremental improvements can generate substantial revenues. Finally, it is not clear that indefinite extension of market exclusivity incentivizes innovation. One study looking at the introduction of novel drugs by brand-name manufacturers found that the loss of market exclusivity protection was the most important predictor of the arrival of a new product.[62]

Another common misperception is that solutions to address unreasonable prices are politically impossible. Recent surveys have found that three-quarters of Americans agree that drug costs are unreasonable.[63] Prescription drugs are essential for medical care, can be transformative, and can also take substantial time and resources to develop. However, high drug prices create burdens for patients and the health care system. Addressing this issue will require fixing the lack of effective competition in the market due to market exclusivity and restrictions on payors that help maintain high prices that are not connected to the value of the products being sold.

62. Graham Stuart & Matthew Higgins, *The Impact of Patenting on New Product Introductions in the Pharmaceutical Industry*, MUNICH PERSONAL REPEC ARCHIVE, AUG. 2007, at 20.

63. *See* Bianca DiJulio et al., *Kaiser Health Tracking Poll: August 2015*, THE HENRY J. KAISER FAMILY FOUND. (Aug. 20, 2015), https://www.kff.org/health-costs/poll-finding/kaiser-health-tracking-poll-august-2015/ (reporting that 72 percent of Americans believed drug costs were unreasonable in a 2015 poll).