PUBLIC HEALTH PRODUCT HOPS

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Pharmaceutical product hops are anticompetitive maneuvers that often represent a last-ditch effort by brand manufacturers to preserve market share in the face of generic competition. An integral part of product life cycle management strategies, product hops may offer marginal benefits to patients but can substantially increase costs to payers and patients alike. Industry advocates, however, maintain that product hops represent essential follow-on research and

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The Author would like to acknowledge the participants in Professor I. Glenn Cohen's Health Law Policy, Bioethics and Biotechnology Workshop at *Harvard Law School* (for helpful comments on an early draft of this manuscript); Professor Aaron S. Kesselheim and members of the Program On Regulation, Therapeutics, And Law ("PORTAL") at Brigham and Women's Hospital and *Harvard Medical School* (for thoughtful questions and insights); attendees at the Works-In Progress Intellectual Property ("WIPIP") 2023 conference in Boston (for feedback on newer policy recommendations); Professors Michael A. Carrier and Daniel G. Aaron (for review and feedback on the manuscript); SLU LAW faculty colleagues attending our spring workshop series (for review and feedback on the manuscript); and SLU LAW students Dr. Edna Besic and Melissa Mann (for research supporting this project).

This Article is dedicated to the memory of Dmitry Karshtedt, JD, PhD, Professor of Law at *George Washington University School of Law* in Washington, D.C. Dmitry's research overlapped with mine, including some of the ideas in this Article and a coauthored project on product hopping. Perhaps due to his training in chemistry and his thirteen patents, Dmitry fundamentally disagreed with the premise that product hops are inherently bad. Some of his patented compounds may have been secondary patents that formed the basis of product hops. His article, *The More Things Change: Improvement Patents, Drug Modifications, and the FDA*, published in the *Iowa Law Review* in 2019, details his conflicting opinions on the issue. In this Article, the first draft of which was completed a week before Dmitry's death in October 2022, I identified case studies to test a theory he inspired: that perhaps certain types of what I term "public health product hops" could be justifiable and perhaps even rewarded or incentivized. Rest well, Dmitry.

development, resulting in the development of novel products that would otherwise never reach the market.

Is there a middle ground between these two diametrically opposed views? Might certain product hops be considered beneficial, perhaps if they furthered important public health interests? Sometimes product hops arise due to safety concerns raised by the U.S. Food and Drug Administration or pressure from other public health agencies. For instance, a push from Congress and the U.S. Environmental Protection Agency to remove chlorofluorocarbons from all consumer and industrial products resulted in a switch from chlorofluorocarbon to hydrofluoroalkane propellants in respiratory inhalers. In another instance, concerns about the opioid crisis fueled the development of abuse-deterrent formulations of opioids as part of a public health response to the crisis. Despite the public health motivations driving each scenario, I find that some public benefit may have been achieved, but at substantial expense to both payers and patients.

I explore the potential benefits of a "public health product hop" in more detail using the recent approval of over-the-counter versions of intranasal naloxone as a case study. This Article develops a framework for rewarding product hops that provide a meaningful and quantifiable public health benefit. In these instances, time-limited patent incentives may more equitably reward manufacturers for advancing important public health goals while ending regulatory incentives for purely profit-driven product hops.

TABLE OF CONTENTS

INTRODUCTION

Pharmaceutical spending in the United States has reached crisis levels, largely due to brand-name drugs and biologics, which account

for 82% of pharmaceutical spending but only 9% of pharmaceutical prescriptions.[1] When profitable pharmaceuticals lose market share due to competition from generic drugs, the financial impact can be dramatic and substantial: a huge benefit to patients who pay dramatically less for more affordable generic versions of their medications but a substantial fiscal loss to brand-name manufacturers as a result of lost market monopolies.[2] As such, pharmaceutical manufacturers will often attempt to limit profit loss from lucrative blockbuster drugs when generics enter the market as part of product life-cycle-management strategies.[3]

One such strategy is product hopping, which occurs when a brand-name manufacturer seeks FDA approval for a new, slightly modified brand-name product that contains the same pharmaceutical ingredient(s).[4] In some cases, the original product is then removed from the market, which can impede market entry of generics, insulate

1. *See* ASS'N FOR ACCESSIBLE MED., U.S. GENERIC & BIOSIMILAR MEDICINES SAVINGS REPORT 9 (Sept. 2022), https://accessiblemeds.org/sites/default/files/2022-09/AAM-2022-Generic-Biosimilar-Medicines-Savings-Report.pdf [https://perma.cc/A9YU-SFZS]. Of note, this report does not account for increased pharmaceutical spending due to COVID-19.

2. *Id.* at 15.

3. *See* Michael A. Carrier & Steve D. Shadowen, *Product Hopping: A New Framework*, 92 NOTRE DAME L. REV. 167, 180 (2016) (demonstrating an example of profit loss limitation); Bret Dickey, Kun Huang & Daniel L. Rubinfeld, *Pharmaceutical Product Hopping: Is There a Role for Antitrust Scrutiny?*, 82 ANTITRUST L.J. 679, 687 (2018) ("[I]t could be profitable for a branded drug manufacturer to remove the old product to preemptively prevent a loss of sales to incoming AB-rated generic products."). An AB rating in the FDA's Orange Book means that the generic product is therapeutically equivalent and may be automatically substituted in place of the branded product at the pharmacy. *Id.* at 683–84. The FDA *Orange Book of Approved Drug Products with Therapeutic Equivalence Evaluations* was first published in 1980 and is now available online at https://www.accessdata.fda.gov/scripts/cder/ob/index.cfm [https://perma.cc/542Z-X9KW]. For AB-rated drug products, "actual or potential bioequivalence problems have been resolved with adequate in vivo and/or in vitro evidence supporting bioequivalence," which enables automatic substitution at most pharmacies. https://www.fda.gov/drugs/development-approval-process-drugs/orange-book-preface [https://perma.cc/23YT-4SYH].

4. *See* Carrier & Shadowen, *supra* note 3, at 167 (defining product hopping as when the manufacturer "(1) reformulates the product in a way that makes the generic non-substitutable and (2) encourages doctors to write prescriptions for the reformulated product rather than the original").

the brand-name market from competition, or both.[5] "Hard switches" like these have triggered Federal Trade Commission (FTC) investigations and injunctions in federal court.[6] In other cases, the old brand-name product remains on the market, but physician detailing and direct-to-consumer advertising drives prescribing of the new product.[7] Though often quite successful in terms of salvaging market share after generic entry, these so-called "soft switches" are often viewed as less anticompetitive than hard switches despite their comparable cost implications.[8]

To entice prescribers and patients, manufacturers may offer co-pay coupons that defray the costs to patients, making such switches easier for patients to justify but creating long-term burdens for health care payers.[9] While most pharmacies automatically substitute generic equivalents to save costs, because the product hop is technically a "new drug," it cannot be automatically substituted for generic drugs in prescriptions because the products are different.[10] Often approved just before market exclusivity on the flagship product ends, product hops tend to offer little more than higher prices, which are passed on to both patients and payers.[11]

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5. *See id.* at 199 (explaining that monopolization occurred when a company "withdr[ew] a successful drug from the market," and "introduc[ed] a reformulated version of that drug," thereby "forc[ing] patients to 'switch to the new version'" and "imped[ing] generic competition" (internal quotes omitted) (quoting New York *ex rel.* Schneiderman v. Actavis PLC, 787 F.3d 638, 660–61 (2d Cir. 2015)).

6. *E.g.*, *New York ex rel. Schneiderman*, 787 F.3d at 663 (affirming an injunction barring a "hard switch").

7. *See* Carrier & Shadowen, *supra* note 3, at 194 (discussing how the U.S. District Court for the District of Columbia interpreted physician detailing and direct-to-consumer advertising as "add[ing] choices").

8. *See id.* ("In a price-disconnected market, switching doctors' prescriptions . . . to a reformulated product . . . significantly impairs consumers' ability to choose a generic product.").

9. *See* Joseph S. Ross & Aaron S. Kesselheim, *Prescription-Drug Coupons—No Such Thing as a Free Lunch*, 369 NEW ENG. J. MED. 1188, 1188 (2013) ("[Sixty-two percent] of coupons were for brand-name medications for which lower-cost therapeutic alternatives were available.").

10. *See* Carrier & Shadowen, *supra* note 3, at 175 (explaining that a pharmacist can only substitute brand drugs for generic versions when it is therapeutically equivalent).

11. *See id.* at 168 ("[S]ome of these switches can significantly decrease consumer welfare, impairing competition from generic drugs to an extent that greatly exceeds any gains from the 'improved' branded product."); *see also* Dickey et al., *supra* note 3, at 680 ("Because product hopping involves potentially beneficial (though

Examples of product hops include switches to extended-release or other formulations of the drug,[12] combination medicines,[13] alterations in either the drug or device component of a drug-device combination,[14] and even switching a product from prescription to over-the-counter ("OTC").[15] In each case, patents on the base compound have usually expired, but manufacturers are often successful at preserving substantial market share.[16]

The prevailing assumption with a product hop is that excess costs and detrimental impact on competition in the marketplace far outweigh the new product's benefits.[17] Is this always the case? I used to think so, until a series of conversations with my late colleague Dmitry Karshtedt in 2017 and 2018 led me to question this blanket presumption. In his 2019 *Iowa Law Review* article titled *The More Things Change: Improvement Patents, Drug Modifications, and the FDA*, Karshtedt

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incremental) improvements of an existing product, some argue that it should generally be viewed as per se lawful and see little role for antitrust intervention. On the other hand, because even a trivial reformulation can substantially inhibit generic competition on the older version of the product, others argue that product hopping can be anticompetitive and should be subject to antitrust scrutiny." (footnotes omitted)).

12. *See* Amy Kapczynski, Chan Park & Bhaven Sampat, *Polymorphs and Prodrugs and Salts (Oh My!): An Empirical Analysis of "Secondary" Pharmaceutical Patents*, PLOS ONE, Dec. 5, 2012, at 1, 3 (analyzing the most common claims made in secondary patent applications, which provide extended exclusivity periods for product hops).

13. Chana A. Sacks, ChangWon C. Lee, Aaron S. Kesselheim & Jerry Avorn, *Medicare Spending on Brand-Name Combination Medications vs Their Generic Constituents*, 320 JAMA 650, 651 (2018).

14. Michael S. Sinha, *Costly Gadgets: Barriers to Market Entry and Price Competition for Generic Drug-Device Combinations in the United States*, 23 MINN. J.L. SCI. & TECH. 293, 293 (2022).

15. *E.g.*, Aaron S. Kesselheim, Jerry Avorn & Ameet Sarpatwari, *The High Cost of Prescription Drugs in the United States: Origins and Prospects for Reform*, 316 JAMA 858, 861 (2016) (demonstrating an example of prescription to over-the-counter product hopping).

16. *See* ALEX BRILL, MATRIX GLOB. ADVISORS, THE COST OF BRAND DRUG PRODUCT HOPPING 3 (Sept. 2020) (citing a study that found evidence of "'deliberate attempts by branded firms to lengthen their monopoly for more lucrative drugs through secondary patents with no chemical compound claim").

17. *See generally* Shaina Vinayek, *Making the Switch: How Little Is too Little in a Competitive Market?*, 16 GEO. J.L. & PUB. POL'Y 339, 351–53 (2018) (conceptualizing the harm of product hops as a delay in competitors being able to enter the market, thereby augmenting the market share of existing monopolies).

argues that some product hops constitute "clinically valuable drug improvements."[18]

Product hops are often couched as offering subtle benefits in patient experience through new formulations or more convenient dosing regimens,[19] but the proliferation of product hops raises the question: are those improvements ever worth the price we end up paying? Might the costs associated with product hops be justifiable if the new product serves a broader public health purpose? And if the cost of these switches can be justified, should we design different incentive structures that offer more modest rewards for such beneficial innovation?[20]

This Article offers a framework for distinguishing between useful and harmful product hops by defining and characterizing certain types of "public health product hops" as beneficial. That is, though product hops are rightfully considered problematic in most situations, there may be public-health considerations driving product hops that justify their increased societal costs.

Part I discusses anticompetitive practices in the pharmaceutical industry that function to extend existing market monopolies while preserving high profit margins. Focusing on pharmaceutical product hops, this Article explores the impact of these practices on various stakeholders, as well as the role those stakeholders play in reigning in product hopping—or at the very least, reducing system costs by making it a less lucrative practice for brand-name manufacturers.

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18. Dmitry Karshtedt, *The More Things Change: Improvement Patents, Drug Modifications, and the FDA*, 104 IOWA L. REV. 1129, 1145 (2019). Dmitry passed in October 2022, but this draft was completed prior to his death, and the questions I pose here are inspired by our conversations.

19. *See* Michael S. Sinha, Edna Besic & Melissa Mann, *Public Health Product Hops*, BILL OF HEALTH (Apr. 24, 2023), https://blog.petrieflom.law.harvard.edu/2023/04/24/public-health-product-hops [https://perma.cc/TQ42-TMV4] (conceding that the incremental changes made to a drug for the purpose of a product hop can provide benefits to patients); *see also* Karen S. Ingersoll & Jessye Cohen, *The Impact of Medication Regimen Factors on Adherence to Chronic Treatment: A Review of Literature*, 31 J. BEHAV. MED. 213, 214 (2008) (asserting that new formulations of medication and dosing simplification may lead to increased medication adherence); Rachel J. Tyson, Christine C. Park, J. Robert Powell, J. Herbert Patterson, Daniel Weiner, Paul B. Watkins & Daniel Gonzalez, *Precision Dosing Priority Criteria: Drug, Disease, and Patient Population Variables*, 11 FRONTIERS PHARMACOLOGY, Apr. 2020, at 1, 2 ("Precision dosing has the potential to elevate the overall quality of drug therapy to provide improved care for patients in whom standard labeled dosages are suboptimal.").

20. I say "modest" here because the incentives discussed *infra* are far less lucrative to manufacturers as compared to a product hop.

Part II introduces the "Public Health Product Hop," considering two historical case studies in which switching product formulations may have occurred for legitimate public health reasons. Section II.A looks at a first case study, respiratory inhalers, which had to pivot away from the use of chlorofluorocarbon ("CFC") based propellants in favor of less environmentally hazardous compounds. The switch was driven by a multinational accord, the Montreal Protocol, as well as the Clean Air Act of 1990.[21] A second case study in Section II.B explores pharmaceutical product hops to abuse-deterrent formulations ("ADFs") of opioids, prescription medications initially developed to treat acute pain syndromes that precipitated a decades-long crisis of misuse, abuse, and overdose deaths. In each case, costs of the product hop far outweighed purported benefits.

In light of these ineffectual "public health product hops," a final case study in Section II.C considers a modern-day example: a switch from prescription to OTC status, which also fits the definition of a product hop. Using the recent conversion of an intranasal formulation of the opioid overdose reversal drug naloxone (Narcan) from prescription to OTC, the Article identifies benefits, such as lower barriers to access, which can be essential during a public health crisis. In this case, there may be losses to the brand-name manufacturer of Narcan that result from the switch, particularly in terms of revenue and market competition.

With an example of a meritorious "public health product hop" in mind, Part III evaluates possible incentives for such switches, particularly if they occur earlier in the market exclusivity period. After a review of existing incentive structures in pharmaceutical policy and their application to public health product hops, the Article considers whether incentives are truly needed—can mandates, rather than incentives, be more successful in inducing performance when public health concerns are dire? A middle ground is proposed: less-outsized incentives for public health product hops, particularly those that meaningfully advance public health objectives.

This Article concludes with overarching thoughts on product hops and dialogue with others who propose alternative strategies to curtail product hops.

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21. Clean Air Act of 1990, 42 U.S.C. § 7401.

I. ANTICOMPETITIVE PRACTICES AND PRODUCT HOPPING

The high drug pricing debate in the United States can almost entirely be linked to market exclusivity periods for brand-name drugs.[22] With a monopoly in place, manufacturers are able to charge whatever the market will bear; only in rare circumstances have there been limits on the brand manufacturer's ability to control the price of a brand-name drug.[23] With broad leverage to set and raise prices, it

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22. I say "almost" because there are exceptions when the prices of generic drugs start to rise, often in settings when the generic market for a particular drug begins to consolidate and become a so-called "niche" drug market (three or fewer manufacturers). *See generally* Frazer A. Tessema, Aaron S. Kesselheim & Michael S. Sinha, *Generic but Expensive: Why Prices Can Remain High for Off-Patent Drugs*, 71 HASTINGS L.J. 1019 (2020) (explaining that for older, off-patent drugs, generics may leave the market over time, and that reduced competition can lead to price spikes that may disrupt access and lead to shortages).

23. Voluntary price concessions have come in the form of an agreement not to raise costs substantially, such as to increase prices by only a single digit annually. In rare cases, public backlash can induce manufacturers to lower prices, as was seen in the Aduhelm controversy, but in other situations, manufacturers will introduce lower cost "authorized generics" to assuage angry patients. *See, e.g.*, Noah Higgins-Dunn, *Why Biogen's Alzheimer's Drug Aduhelm Is so Controversial*, CNBC NEWS (Jan. 4, 2022, 11:55 AM), https://www.cnbc.com/2022/01/04/why-biogens-alzheimers-drug-aduhelm-is-so-controversial-.html [https://perma.cc/CZL2-V5BC] (stating that Biogen will decrease the price of Aduhelm after its high list price and under-performing sales); *Mylan Launches the First Generic for EpiPen® (Epinephrine Injection, USP) Auto-Injector as an Authorized Generic*, MYLAN (Dec. 16, 2016), https://investor.mylan.com/news-releases/news-release-details/mylan-launches-first-generic-epipenr-epinephrine-injection-usp [https://perma.cc/7TJG-TQ3R] (announcing an authorized generic version of the EpiPen at half the wholesale acquisition cost citing consumer concerns about rising drug costs). Most recently, the "big three" insulin manufacturers (Eli Lilly & Co., Novo Nordisk, and Sanofi) have all voluntarily agreed to steep price concessions for insulin products. *See* Ilena Peng, *Sanofi Follows Lilly, Novo in Cutting Insulin Prices*, BLOOMBERG (Mar. 16, 2023, 5:10 PM), https://www.bloomberg.com/news/articles/2023-03-16/sanofi-cuts-insulin-prices-up-to-78-following-lilly-novo [https://perma.cc/6CET-ANVA] (highlighting how increased pressure from lawmakers and advocates was a key factor in the "big three's" decision to reduce prices). The Inflation Reduction Act will also impact drug pricing, though many of the individual provisions that specifically address drug prices do not go into effect until 2024, 2026, and 2027. *See* Juliette Cubanski, Tricia Neuman & Meredith Freed, *Explaining the Prescription Drug Provisions in the Inflation Reduction Act*, KFF (Jan. 24, 2023), https://www.kff.org/medicare/issue-brief/explaining-the-prescription-drug-provisions-in-the-inflation-reduction-act [https://perma.cc/7WQH-AZSQ] (listing the prescription drug provisions included in the Inflation Reduction Act and their implementation dates); Anna Kaltenboeck, *What the Inflation Reduction Act's Reforms to Medicare Part D Mean for*

comes as no surprise that brand-name drugs are primary drivers of U.S. drug spending.[24] As Kesselheim and his colleagues note in the *Journal of the American Medical Association*: "The only form of competition that consistently and substantially decreases prescription drug prices occurs with the availability of generic drugs, which emerge after the monopoly period ends."[25] As such, any attempt by a brand manufacturer to forestall generic entry should be viewed with skepticism.

Product hops are often seen as anticompetitive in that they can limit uptake of generic drugs, which disrupts free-market dynamics and generates excess spending.[26] Brand-name drug producers ought to justify increased costs to patients and payers by explaining the purported additional benefits of product hops. Yet, in most cases, improvements in clinical care are marginal or inframarginal when compared to the outsized costs associated with the maintenance of monopoly pricing structures.[27] These costs affect everyone in the health care system, including patients.[28] In some cases, manufacturers will offer drug coupons or contribute to patient assistance programs to defray out-of-pocket expenditures for patients.[29]

Prescription Drug Prices, HEALTH AFF. FOREFRONT (Jan. 20, 2023), https://www.healthaffairs.org/content/forefront/inflation-reduction-act-s-reforms-medicare-part-d-mean-prescription-drug-prices [https://perma.cc/7HN2-SVT2] (discussing how the Inflation Reduction Act addresses rising list prices of drugs by capping beneficiary cost sharing).

24. *See* ASS'N FOR ACCESSIBLE MED., *supra* note 1, at 9 (reporting that brand-name companies accounted for 82% of the share of total medicine spending in 2021).

25. Kesselheim et al., *supra* note 15, at 861.

26. *See* Carrier & Shadowen, *supra* note 3, at 168 ("[Product hopping] impair[s] competition from generic drugs to an extent that greatly exceeds any gains from the 'improved' branded product.").

27. *See id.* at 183 (asserting that high drug pricing is not caused by medical innovation but market failure).

28. *See id.* ("The industry's profit pie does not get substantially smaller; it just gets split among more manufacturers. . . . [C]onsumers pay supracompetitive prices regardless of which prescription they get.").

29. *See* Ross & Kesselheim, *supra* note 9, at 1188 ("Manufacturers use coupons to reimburse patients for this difference in copayments when they buy brand-name medications . . . ."); *see also* Michael S. Sinha, Aaron S. Kesselheim & Christopher T. Robertson, *Patient Assistance Programs and the Anti-Kickback Statute: Charting a Pathway Forward*, 327 JAMA 1231, 1231 (2022) ("Patient assistance programs provide subsidies that allow patients to meet their out-of-pocket payment obligations when filling prescriptions for expensive drugs.").

A. Definition and Impact

Product hopping can be "broadly characterized as a branded manufacturer introducing a minor change to an existing prescription drug product and substantially shifting sales to the reformulated product, with the effect of inhibiting emerging competition from a generic version of the original branded product."[30] Though the "minor change" could be as significant as the introduction of a new drug delivery device, the therapeutic advantage to patients is often not substantial.[31]

Scholars have described the controversy relating to product hops in the following way:

> Because product hopping involves potentially beneficial (though incremental) improvements of an existing product, some argue that it should generally be viewed as per se lawful and see little role for antitrust intervention. On the other hand, because even a trivial reformulation can substantially inhibit generic competition on the older version of the product, others argue that product hopping can be anticompetitive and should be subject to antitrust scrutiny.[32]

The degree to which a product hop can be deemed anticompetitive depends on the circumstances in which the switch occurs.[33] In some cases, the brand-name manufacturer might attempt to remove its predecessor from the market and switch all patients to the new product—this is known as a hard switch.[34] In this circumstance, the brand-name manufacturer benefits from rapid uptake of its new costly

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30. Dickey et al., *supra* note 3, at 680. Carrier and Shadowen define product hopping as follows:

> Product hopping, which is also known as "evergreening" or "line extension," refers to "a drug company's reformulation of its product" and encouragement of doctors to prescribe the reformulated, rather than original, product. Under our definition, a brand manufacturer engages in a "product hop" by combining two actions: (1) reformulating the product in a way that makes a generic version of the original product not substitutable; and (2) encouraging doctors to write prescriptions for the reformulated rather than the original product, i.e., switching the prescription base from the original to the reformulated product.

Carrier & Shadowen, *supra* note 3, at 171 (footnotes omitted).

31. *See id.* at 176 (describing how manufacturers making minor changes like switching to a tablet deprives consumers from substantial pricing benefits).

32. Dickey et al., *supra* note 3, at 680 (footnotes omitted).

33. *See, e.g.*, Carrier & Shadowen, *supra* note 3, at 192–205 (examining five cases in which a product hopping analysis was applied).

34. *See id.* at 170 (defining a hard switch as "those in which the brand withdraws the original product from the market").

drug while generics can no longer compete for that patient population.[35] Hard switches are closely scrutinized by regulators and courts.[36]

By contrast, soft switches do not involve market removal of the predecessor compound or other overtly anticompetitive tactics, and therefore receive far less scrutiny.[37] As Carrier and Shadowen note, "[c]ourts and commentators have drawn rigid distinctions between hard switches, viewed as anticompetitive because the brand removes the original drug from the market, and soft switches, viewed as not concerning because the original remains on the market."[38] However, they note that this is an oversimplification: soft switches can still have considerable economic impact via the extraction of market share from would-be generic competitors.[39]

B. Impact on Patients

A new product derived from a successful brand-name drug can offer tangible benefits to some patients. For instance, an extended-release formulation may decrease the frequency with which a medication is taken, which could improve medication adherence, particularly for certain vulnerable populations.[40]

In the case of Namenda (memantine), development of the extended release formulation meant that patients with cognitive impairment would need to take the medication once daily as opposed to twice a

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35. *See id.* at 217–18 ("According to the well-established economics of the industry, absent the reformulations, the generics in both cases would have captured at least 85% of unit sales. With a product withdrawal in *Tricor*, they gained only 2%.").

36. *See infra* Section I.E.

37. *See* Michael A. Carrier & Carl J. Minniti III, *Biologics: The New Antitrust Frontier*, 2018 U. ILL. L. REV. 1, 31 (2018) (explaining how soft switches are subject to less judicial scrutiny than hard switches because of the belief that soft switches allow the patient a modicum of choice between the original and reformulated drug and are therefore less coercive).

38. Carrier & Shadowen, *supra* note 3, at 217. The authors rightly point out that the dichotomy between hard switches (bad) and soft switches (good) is oversimplified, instead proposing a "no-economic-sense" analysis focused on the economic impact of the product hop. *Id.*

39. *Id.* at 211. The authors propose a "no-economic-sense analysis" that asks "whether conduct allegedly maintaining a monopoly by excluding nascent competition 'likely would have been profitable if the nascent competition flourished and the monopoly was not maintained.'" *Id.*

40. *See* Ingersoll & Cohen, *supra* note 19, at 214 ("[I]t is possible that medications formulated to reduce or simplify dosing may result in increased adherence.").

day, which could ostensibly provide benefits for both patients and their caretakers.[41] For such patients, medications often have to be hidden in applesauce or pudding to ensure adherence, so any reduction in pill burden could significantly improve care.[42] Combination medications, which are common among cardiovascular and infectious diseases therapies, often tout reduction in pill burden as a primary benefit as well.[43]

Altered formulations or dosing regimens for injectable medications may also offer some patient benefit. For instance, Copaxone (glatiramer acetate) switched from a daily dosing regimen to a three-times-weekly injectable dosing regimen.[44] Citrate-free formulations of Humira (adalimumab) also stand to benefit patients through less painful injections.[45] In each case, the primary motivation was to extend market exclusivity, but some clinical benefit derived as well.[46] How much patient benefit is needed to justify the costs associated with these new brand-name products, and what constitutes a reasonable reward for such improvements?

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41. 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, 340 (2016).

42. *See* Gary Small & Bruno Dubois, *A Review of Compliance to Treatment in Alzheimer's Disease: Potential Benefits of a Transdermal Patch*, 23 CURRENT MED. RSCH. & OP. 2705, 2706 (2007) ("Approximately three of four [Alzheimer's disease] patients need help managing and taking their medications, and such medication management is associated with caregiver stress."); *see also* Kelly M. Makino & Anton P. Porsteinsson, *Memantine: A Treatment for Alzheimer's Disease with a New Formulation*, 7 AGING HEALTH 349, 351 (2011) (touting the benefits of an extended-release formulation of memantine to include the following: "For patients who have difficulty swallowing, the capsules may be opened so that the contents can be administered as a mixture in apple sauce").

43. *See* Sacks et al., *supra* note 13, at 655 (suggesting that reducing pill burden can improve patient adherence).

44. Benjamin N. Rome, Frazer A. Tessema & Aaron S. Kesselheim, *US Spending Associated with Transition from Daily to 3-Times-Weekly Glatiramer Acetate*, 180 JAMA: INTERNAL MED. 1165, 1165 (2020).

45. *See* Sinha, *supra* note 14, at 337 (illustrating how anticompetitive behavior, such as reformulating drugs to block biosimilar entry into the market, can still offer tangible patient benefits).

46. *See id.* (noting that another effect of these products was simplifying patient self-administration).

C. Impact on Payers

Because of the many stakeholders involved in the prescription of a pharmaceutical product, there is a disconnect between the individual writing the prescription and the entities paying for it. Physicians are often unaware of the costs of medications when writing prescriptions, and patients are often unaware of more affordable generic alternatives.[47] This can be true for product hops like extended-release formulations, which are traditionally launched just prior to the timing of generic entry.[48] Pharmaceutical manufacturers heavily promote their new products to both prescribers and patients, seeking to win favor in competitive markets when there are often cheaper alternatives available.[49]

Pharmacy benefit managers ("PBMs") and pharmaceutical wholesalers are "middlemen" between pharmaceutical manufacturers and insurance companies.[50] Though they were initially set up to improve administrative efficiency, the three largest PBMs and the

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47. Steven Reichert, Todd Simon & Ethan A. Halm, *Physicians' Attitudes About Prescribing and Knowledge of the Costs of Common Medications*, 169 JAMA 2799, 2802 (2000) (noting "80% often felt unaware of the actual costs of medications, and only 13% reported ever having any formal education about the cost of medications").

48. *See* News Release, Fed. Trade Comm'n, FTC Files Amicus Brief Explaining that Pharmaceutical "Product Hopping" Can Be the Basis for an Antitrust Lawsuit (Nov. 27, 2012), https://www.ftc.gov/news-events/news/press-releases/2012/11/ftc-files-amicus-brief-explaining-pharmaceutical-product-hopping-can-be-basis-antitrust-lawsuit [https://perma.cc/P9EV-NY9P] (explaining the process of product-hopping); Sacks et al., *supra* note 13, at 655 (explaining that "creating new brand name combination products offers an opportunity to extend market exclusivity" and that manufacturers tend to launch these products before the generic single active ingredient drug enters the U.S. market).

49. *See* Lisa M. Schwartz & Steven Woloshin, *Medical Marketing in the United States, 1997–2016*, 321 JAMA 80, 84 (2019) (detailing medical marketing trends in the United States). Importantly, even though Americans may feel inundated by direct-to-consumer advertising in lay media, promotion to physicians is substantially higher than direct-to-consumer spending. *See id.* at 91, 93 (concluding that most medical marketing spending is directed towards health care professionals); *see also* Michael S. Sinha, Aaron S. Kesselheim & Jonathan J. Darrow, *Pharmaceutical Advertising in Medical Journals: Revisiting a Long-Standing Relationship*, 153 CHEST J. 9, 9 (2018) (finding that print-based advertising in medical journals is one such medium to reach physicians).

50. *See* Dylan Scott, *The Mysterious Middlemen Being Blamed for America's Sky-High Drug Prices*, VOX (May 10, 2023, 7:00 AM), https://www.vox.com/2023/5/10/23709448/what-are-pbms-pharmacy-benefit-managers-bernie-sanders [https://perma.cc/FN8N-VNPM] (discussing how the role of PBMs includes determining what patients pay for medications, managing insurance benefits, dictating which drugs are covered, and negotiating discounts or rebates with manufacturers).

three largest wholesalers have profited substantially from this distribution scheme.[51] PBMs do not always prefer generics; in some cases, PBMs may stand to benefit from the continued use of a brand-name medication over a generic alternative, given that rebates from the manufacturer can be lucrative.[52] This could provide enough of an incentive to favorably tier the product hopped version, even when cheaper alternatives are available.

Despite the limited benefits to patients, the costs remain astounding. A study in the *Journal of American Medical Association* looked at federal spending in Medicare on branded combination medications for which generic alternatives exist.[53] The authors identified $925 million in excess spending on these drugs in 2016 alone; many of these products are considered to be product hops.[54] Though common sense may suggest that physicians would prescribe less costly alternatives when they become available, pharmaceutical sales practices may heavily influence the decision to continue prescribing brand-name medications to patients.[55] In many cases, physicians simply aren't aware of the availability of cheaper generic alternatives.

D. Influence on Prescribers

Pharmaceutical manufacturers spend billions of dollars promoting their products to physicians.[56] Pharmaceutical detailers extol the virtues of new formulations, touting ease of administration, extended

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51. For a historical look at PBMs, see Stephan L. Burton, Lauren Randel, Karen Titlow & Ezekiel J. Emanuel, *The Ethics of Pharmaceutical Benefit Management*, 20 HEALTH AFFS. 150 (2001) and Nancy L. Yu, Preston Atteberry & Peter B. Bach, *Spending on Prescription Drugs in the US: Where Does All the Money Go?*, HEALTH AFFS. (July 31, 2018), https://www.healthaffairs.org/do/10.1377/forefront.20180726.670593 [https://perma.cc/NZM8-W29Y].

52. *See* Elizabeth Seeley & Aaron S. Kesselheim, *Pharmacy Benefit Managers: Practices, Controversies, and What Lies Ahead*, COMMONWEALTH FUND ISSUE BRIEF, Mar. 2019, at 1, 1–3, https://www.commonwealthfund.org/sites/default/files/2019-03/Seeley_pharmacy_benefit_managers_ib_v2.pdf [https://perma.cc/H57C-VKGV] (noting that "tiering or other utilization management strategies were used to favor on-patent brand-name drugs over less expensive (i.e., potentially generic) drugs that are just as clinically useful").

53. Sacks et al., *supra* note 13, at 651.

54. *See id.* at 653 (noting that prescribing generic versions of brand name drugs could have reduced spending by an estimated $2.7 billion between 2011 and 2016).

55. *Id.* at 655.

56. *See generally* Schwartz & Woloshin, *supra* note 49 (finding that medical marketing spending reached $29.9 billion in 2016).

duration of action, or other features of the modified product.[57] In addition, a company may pursue other complementary strategies, including the provision of free drug samples of only the new formulation or of co-pay coupons to patients to lower their out-of-pocket costs.[58] In light of these various incentives and the relative obscurity of drug prices at the point of care, physicians may be swayed to prescribe brand-name product hops when generic equivalents are readily available.

Electronic health records and other tools are poorly designed to help inform cost-conscious prescribing at the time of the patient encounter.[59] Online references like GoodRx provide some information, but not for patients who have prescription drug coverage.[60] A good rule of thumb is that the brand-name product will cost more than the generic, but physicians are often unaware of the availability or cost of generics when prescribing.[61]

E. Government Response

Two main entities, the U.S. Food and Drug Administration (FDA) and the FTC, are tasked with reigning in anticompetitive practices in

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57. *See, e.g.*, Ben Popken, *Mylan's Upgraded EpiPen Torn Apart by Experts*, NBC NEWS, https://www.nbcnews.com/business/consumer/mylan-says-it-upgraded-epipen-2009-so-experts-looked-inside-n652651 [https://perma.cc/52ZD-8GGV] (last updated Sept. 30, 2016, 5:12 PM) (including in its list of upgrades to the Mylan EpiPen, a new one-step carrying case for quick removal, safer needle exposure, color changes for easier identification, and plans to increase its shelf-life).

58. Brief for Amicus Curiae Federal Trade Commission Supporting Plaintiff-Appellant at 8–9, Mylan Pharms. Inc. v. Warner Chilcott PLC, 838 F.3d 421 (3d Cir. 2015) (No. 15-2236) [hereinafter *FTC Amicus Brief*].

59. David Blumenthal, *The Electronic Health Record Problem*, COMMONWEALTH FUND (Dec. 13, 2018), https://www.commonwealthfund.org/blog/2018/electronic-health-record-problem [https://perma.cc/H64W-Q3FD] (reporting that physicians complain about how "electronic records are clunky, poorly designed, hard to navigate, and cluttered"). From a personal perspective, when I trained as an internal medicine resident, I recall utilizing a feature in the electronic health record system Epic that informed prescribers of the prices of medications prior to e-prescribing them. That feature appears to have been short-lived but offered needed price transparency at the point of care.

60. GOODRX HOLDINGS, INC., https://www.goodrx.com [https://perma.cc/76QP-BXCB].

61. Mariana P. Socal, Ge Bai & Gerard F. Anderson, *Factors Associated with Prescriptions for Branded Medications in the Medicare Part D Program*, 4 JAMA: NETWORK OPEN, Mar. 2, 2021, at 1, 9 ("Efforts to improve physicians' perception of generic medications, [and] raising their awareness of the availability of generics . . . might be effective in enhancing generic use.").

the pharmaceutical industry.[62] The FDA has been monitoring the impact of product hopping and has sought comment on issues relating to product hopping.[63] That said, the FDA rarely rejects new drug applications other than on the basis of safety and efficacy. If there is limited additional evidence related to these two criteria, manufacturers can rely on data from the original product's application.[64]

The FTC has been more active with regard to product hopping, noting that "[i]n the pharmaceutical industry . . . the success of a product switching scheme does not depend on whether consumers prefer the reformulated version of the product over the original, or whether the reformulated version provides any medical benefit."[65] In 2012, the FTC prepared an amicus brief asserting that hard switches "forc[e] consumers to switch to the reformulated brand drug and enabl[e] the branded company to keep its market exclusivity and prevent[] consumers from obtaining the benefits of generic competition."[66] A second amicus brief, filed in 2015, raised concerns that "manufacturer[s] might restrict or eliminate the supply of the original formulation, increase its effective price to patients, or flood physician offices with free samples of the revised formulation but not

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62. *See* Dickey et al., *supra* note 3, at 680–81, 684 (discussing agency scrutiny of potentially anticompetitive drug manufacturing practices).

63. *See, e.g.*, Meeting Notice and Request for Comments, 82 Fed. Reg. 28493 (June 22, 2017). My co-authored public comment to this docket is available at: Ameet Sarpatwari, Michael S. Sinha & Aaron S. Kesselheim, Comment Letter on Proposed Rule on Administering Hatch-Waxman Amendments (Nov. 20, 2017), https://www.regulations.gov/document/FDA-2017-N-3615-0092 [https://perma.cc/9YYT-EHVP] (discussing anticompetitive practices by brand-name manufacturers and making recommendations for FDA to improve trust in generic brands).

64. 21 C.F.R. § 314.125 (listing permitted reasons for FDA refusal); *see also* Harinder Singh Chahal, Sanjana Mukherjee, Daniel W. Sigelman & Robert Temple, *Contents of US Food and Drug Administration Refuse-to-File Letters for New Drug Applications and Efficacy Supplements and Their Public Disclosure by Applicants*, 181 JAMA: INTERNAL MED. 522, 522 (2021) (84.5% of FDA refusal reasons were scientific deficiencies related to efficacy, safety, and drug quality).

65. FTC, INTERVIEW WITH COMMISSIONER WILSON AND BARRY NIGRO ON THE HOUSE JUDICIARY REPORT 6 n.27 (2020) (quoting Federal Trade Commission's Brief as Amicus Curiae at 12, Mylan Pharms., Inc., v. Warner Chilcott Pub. Ltd. Co., No. 12-CV-3824, 2015 WL 1736957 (E.D. Pa. Apr. 16, 2015), *aff'd*, 838 F.3d 421 (3d Cir. 2016)), https://www.ftc.gov/system/files/documents/public_statements/1588040/aba_interview_with_commissioner_wilson_on_the_house_judiciary_report.pdf [https://perma.cc/VDV6-SY2C].

66. FTC, *supra* note 48.

the original to divert prescriptions to the revised formulation."[67] In 2019, the FTC settled with Reckitt Benckiser, manufacturer of Suboxone film, for $50 million after allegations that the company engaged in product hopping from tablet to film to thwart generic competition.[68]

II. PUBLIC HEALTH PRODUCT HOPS

Despite the market disruptions and excess spending driven by product hops, Karshtedt maintained that efforts focused on "better[ing] the pioneering drug in some specific dimension, such as improving patient compliance or reducing side effects," deserved additional market incentives.[69] While I remain skeptical that individual patient benefits can justify the market disruptions caused by product hops, I hypothesize that certain product hops, focused on broader public health benefit, could be justifiable.

The "public health product hop" I propose will alter the calculation of benefit and harm by incorporating the consideration of public health benefits. Given the overt anticompetitive impacts of most product hops, regulators and courts in these unique situations should seek to determine whether the public health benefit could be significant enough to outweigh the known harms of product hopping. I now turn to two relevant case examples of public health product hops that highlight the challenges of balancing these considerations, then explore a more recent third example that may help pave a path forward.

A. Case 1: CFC to HFA Respiratory Inhaler Switches

CFCs are a class of chemical compounds that were used industrially in refrigeration systems, aerosol sprays, and polymer foams, among other uses.[70] They were initially developed as nontoxic alternatives to

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67. *FTC Amicus Brief*, *supra* note 58, at 8–9.

68. Press Release, Fed. Trade Comm'n, Reckitt Benckiser Group PLC to Pay $50 Million to Consumers, Settling FTC Charges that the Company Illegally Maintained a Monopoly over the Opioid Addiction Treatment Suboxone (July 11, 2019), https://www.ftc.gov/news-events/news/press-releases/2019/07/reckitt-benckiser-group-plc-pay-50-million-consumers-settling-ftc-charges-company-illegally [https://perma.cc/UX2T-GJUV].

69. Karshtedt, *supra* note 18, at 1222.

70. *See generally Chlorofluorocarbon*, SCI. DIRECT, https://www.sciencedirect.com/topics/engineering/chlorofluorocarbon [https://perma.cc/DJJ4-NATV] (providing background on CFC uses).

refrigerants that were used in the 1920s—Frigidaire received the first patent for CFCs,[71] and DuPont sold the product under the trade name Freon.[72] Soon thereafter, Freon gained widespread use in refrigerators and air conditioners.[73] Household uses for CFCs, including in medical products, emerged in the 1940s and 1950s.[74] CFCs gained an important new use as propellants in respiratory devices: when used as directed, CFC plumes could efficiently deliver an aerosolized drug past a patient's oropharynx and into the lungs upon deep inspiration, which allowed for use of lower doses to generate the same therapeutic efficacy.[75] CFCs were thus integral to the early development of pressurized metered dose inhalers ("pMDIs" or "MDIs"), which are now standard of care in treating a variety of respiratory conditions.[76]

1. Emerging evidence for CFCs as environmental pollutants

Though CFCs were safe for use in most applications and inert in the lower atmosphere, in 1974, two chemists from the University of California found that, after photolytic decomposition by UV radiation, free chlorine molecules from CFCs could rapidly destroy ozone in the stratosphere.[77] The process was catalytic, in that one single atom of chlorine could destroy up to 100,000 molecules of ozone.[78]

As a consequence, in 1987, a global consortium of 148 countries signed the Montreal Protocol on Substances that Deplete the Ozone

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71. U.S. Patent No. 1,886,339 (filed Dec. 31, 1928).

72. James W. Elkins, *Chlorofluorocarbons (CFCs)*, in CHAPMAN & HALL ENCYC. OF ENV'T SCI. 78–80 (David E. Alexander & Rhodes W. Fairbridge eds., 1999).

73. *Id.*

74. *Id.*

75. *See* Stephen W. Stein & Charles G. Thiel, *The History of Therapeutic Aerosols: A Chronological Review*, 30 J. AEROSOL MED. & PULMONARY DRUG DELIVERY 20, 27 (2017) (detailing the history and modernization of therapeutic aerosols, specifically with regards to asthma treatment); DOUGLAS GARDENHIRE, DAVE BURNETT, SHAWNA STRICKLAND & TIMOTHY MYERS, A GUIDE TO AEROSOL DELIVERY DEVICES FOR RESPIRATORY THERAPISTS, 2, 4 (4th ed. 2017) (detailing, *inter alia*, the advantages and disadvantages of inhaled aerosol drugs). Among the products that utilized CFCs as propellants was Primatene Mist, a medication to treat asthma that had been available OTC for over fifty years. *CDER Conversation: Safely Using the Newly Available OTC Asthma Inhaler Primatene Mist*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/drugs/news-events-human-drugs/cder-conversation-safely-using-newly-available-otc-asthma-inhaler-primatene-mist [https://perma.cc/G3FZ-BLUG] (last updated Nov. 9, 2018).

76. *See generally* Stein & Thiel, *supra* note 75 (discussing role of CFC propellants in medical aerosol development).

77. Elkins, *supra* note 72.

78. *Id.*

Layer.[79] Early amendments to the Protocol allowed exemptions for certain "essential uses," including the use of pMDIs in the treatment of respiratory conditions.[80] Industrial uses of CFCs were phased out on January 1, 1996, but in its codification of the responsibilities of the Montreal Protocol within the Clean Air Act of 1990, Congress emphasized that CFC pMDIs should be phased out only when adequate alternatives are available.[81]

Despite this insistence on waiting for readily available alternatives, in 1996, an FDA-proposed rule sought to remove the essential use of CFC-based pMDIs, thereby making them illegal to produce in the United States.[82] At a hearing discussing the proposed rule, Congressman George Brown, Jr. (D-CA) noted that the plan was to "work to implement a phaseout that ensures that we have a substantial number of patient accepted non-CFC products on the market."[83] Congressman Brown expressed confidence that "[w]ith one non-CFC MDI approved and several in the agency's review pipeline, . . . these companies will continue to be innovators for the development of new MDIs for the patients who need them."[84]

Representative John Dingell (D-MI) noted the following in prepared testimony:

> In the Clean Air Act Amendments, we made the decision to ban CFCs and other substances that threaten the ozone layer. But we also recognized the vital role of inhalers using CFCs in delivering medicine to those with serious respiratory problems. As a result, in section 604(d)(2) of the Clean Air Act, Congress provided a specific "critical use" exemption from the phase out of CFCs in the United

79. *The Montreal Protocol on Substances that Deplete the Ozone Layer*, U.N. ENV'T PROGRAMME, https://ozone.unep.org/treaties/montreal-protocol [https://perma.cc/32M2-9U8P]. The Montreal Protocol originally called for a 50% reduction in the production and consumption of CFCs by 2000 for developed countries. *The Montreal Protocol*, CTR. FOR PUB. IMPACT (Sept. 3, 2019), https://www.centreforpublicimpact.org/case-study/the-montreal-protocol [https://perma.cc/J7FT-GXA5].

80. *Annex I: Essential Use Exemptions*, U.N. ENV'T PROGRAMME, https://ozone.unep.org/meetings/sixth-meeting-parties-montreal-protocol/decisions/annex-i-essential-use-exemptions [https://perma.cc/CC4T-4CU8]; *Exemptions to the Phaseout*, EPA, https://www.epa.gov/ods-phaseout/exemptions-phaseout [https://perma.cc/WP99-4QEV] (last updated Jan. 3, 2023).

81. *Exemptions to the Phaseout*, *supra* note 80.

82. 40 C.F.R. § 82.64(c) (1996); 61 Fed. Reg. 15699 (Apr. 9, 1996).

83. *Regulatory Efforts to Phaseout Chlorofluorocarbon-Based Metered Dose Inhalers: Hearing on H.R. 2968 Before the Subcomm. on Health and Env't of the Comm. on Com.*, 105th Cong. (1998) (statement of Congressman Brown).

84. *Id.*

> States for medical devices including metered-dose inhalers. This exemption lasts so long as the commissioner of the FDA deems it necessary.[85]

Representative Dingell criticized the EPA for pressing the FDA to urgently withdraw these medicines, noting: "There is only one Agency charged by law with the job of determining if and when safe and effective alternative inhalers are available, and that is the FDA."[86]

Dingell also highlighted the importance of cost and access in his testimony:

> FDA must adopt a transition approach that scrupulously guards the safety of patients. This means that products should not be withdrawn from the market unless and until there are proven, safe and effective non-CFC products . . . . FDA should also look at costs. While reformulated drug[s] may medically substitute for a current generic brand, they may not be "available" to the general public if they cost two or three times as much.[87]

Representative Patrick Kennedy (D-RI), who was first diagnosed with asthma as a child, pointed to "a cynical lobbying campaign by drug company lobbyists concerned about their company's share of a respiratory drug market estimated at nearly $3 billion a year in sales."[88] Kennedy highlighted that the amount of CFCs emitted by inhalers amounts to about 1.5% of all CFCs and noted that "[i]t's such a minuscule amount that it's really crazy to be thinking about the need for exemptions for CFCs."[89]

At the time, Christopher Smith (R-NJ) and Cliff Stearns (R-FL) introduced a bill in opposition to the Proposed Rule. The bill provided that the FDA could not remove a product until a non-CFC product was either comparable or superior to its non-CFC replacement, and that the FDA "shall not prohibit the manufacture, sale, or distribution of any CFC MDI product on the basis that it is 'adulterated' or 'misbranded.'"[90]

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85. *Id.* (statement of Congressman Dingell).

86. *Id.*

87. *Id.*

88. Bill McAllister, *Ozone, Asthma and Inhalers: Drugmaker's Lobbying Assailed*, WASH. POST (May 6, 1998), https://www.washingtonpost.com/archive/politics/1998/05/06/ozone-asthma-and-inhalers-drugmakers-lobbying-assailed/bb559343-861d-489c-82ee-322a5740d2a4 [https://perma.cc/2KG5-83C8].

89. *Id.*

90. H.R. 2968, 105th Cong. (1997). To require the Secretary of Health and Human Services to take no further action on proposed regulation relating to the use of chlorofluorocarbons in metered-dose inhalers. *Id.*

By 2008, the FDA determined the following:

> Two albuterol MDIs that do not use an ODS [ozone-depleting substance] have been marketed for more than [three] years. FDA has determined that the two non-ODS MDIs will be satisfactory alternatives to albuterol MDIs containing ODSs and is removing the essential-use designation for albuterol MDIs as of December 31, 2008. Albuterol MDIs containing an ODS cannot be marketed after this date.[91]

Despite the fact that two brand-name products do not make for a competitive and cost-effective market, this was enough for the FDA to justify broad product removal.[92] The only OTC CFC pMDI for asthma, Primatene Mist, was withdrawn from the market in December 2011.[93] The manufacturer obtained approval for a new formulation of Primatene Mist using hydrofluoroalkanes ("HFAs") in November 2018, nearly seven years after its CFC-based formulation was removed from the market.[94]

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91. Use of Ozone-Depleting Substances; Removal of Essential-Use Designations, 70 Fed. Reg. 17168 (Apr. 4, 2005).

92. *See* Olivier J. Wouters, William B. Feldman & S. Sean Tu, *Product Hopping in the Drug Industry—Lessons from Albuterol*, 387 NEW ENG. J. MED. 1153, 1153 (2022) ("Over the quarter-century since the first HFA-containing albuterol inhalers were approved, manufacturers have reaped immense financial rewards. The resulting 'product hops' to the new albuterol inhalers generated approximately $14 billion in U.S. sales between 2007 and 2021.").

93. Salynn Boyles, *Asthma Specialists Attack Return of Primatene Mist*, MED PAGE TODAY, https://www.medpagetoday.com/allergyimmunology/asthma/80863 [https://perma.cc/LB9C-J3ZD] (last updated July 8, 2019). OTC medication access is important for pharmacoequity. Patients with limited access to healthcare services, either due to uninsurance or other factors, may rely on products available on pharmacy shelves, even if they are less effective at treating asthma compared to prescribed alternatives containing albuterol. *See id.* (noting patients may be unable to keep their asthma under control with some OTC drugs).

94. Edward M. Kerwin, Donald P. Tashkin, Phillip E. Korenblat, Leon S. Greos, David S. Pearlman & George W. Bensch et al., *Long-term Safety and Efficacy Studies of Epinephrine HFA Metered-Dose Inhaler (Primatene® Mist): A Two-Stage Randomized Controlled Trial*, 58 J. ASTHMA 633, 633–34 (2021); *FDA-Approved Drugs*, U.S. FOOD & DRUG ADMIN., https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=016126 [https://perma.cc/P94D-7DAR] (listing the filing for Primatene Mist and categorizing it as discontinued); Letter to Gisela Sharp, Senior Manager at Armstrong Pharms., Inc., from Theresa Michele, MD, Dir. in the Nonprescription Drug Prods. at the FDA (Nov. 7, 2018) (on file with FDA), https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2018/205920Orig1s000ltr.pdf [https://perma.cc/PP97-6S78] (approving the amended drug application).

2. Role of inhaler manufacturers in the switch

The first HFA product, 3M's Proventil HFA, was introduced in 1996 and had the non-CFC market to itself for some time.[95] In fact, patent exclusivity, coupled with a regulatory push to use HFA-134a as a propellant in reformulated products, created a troubling situation.[96] As Charles Duan notes,

> 3M . . . held patents on the only alternative approved propellant, HFA-134a. Mandating CFC-free inhalers replaced a robustly competitive generic market with patent-backed monopoly control. The pharmaceutical industry reaped nearly a billion dollars per year at the expense of asthma patients, and some low-income asthmatics could no longer afford their medication.[97]

Stephen Stein, an aerosol scientist at 3M at the time, had a different take—innovating non-CFC inhalers gave the industry an "opportunity to improve upon a technology that really had kind of stagnated over the past decades."[98] Notably, "the older devices left much of the drug in the mouth and throat, so researchers made changes to allow a larger proportion of the drug to reach the lungs, such as altering the inhalers so that they release smaller particles."[99]

Scientists from Glaxo Wellcome—manufacturers of two CFC metered dose inhalers at the time—described the exemption from the CFC switch as an opportunity.[100] The push to eliminate CFCs "provid[ed] a time period to develop alternative propellants. Subsequent research led to the development of [HFAs], and 1,1,1,2 tetrafluoroethane (HFA 134a) was chosen as the replacement propellant for pMDIs containing salbutamol (Ventolin™) and fluticasone propionate (Flixotide™)."[101]

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95. *FDA-Approved Drugs*, U.S. FOOD & DRUG ADMIN., https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=020503 [https://perma.cc/WP9B-2W2W] (providing the application for Proventil-HFA and listing the first filing date as December 26, 1996).

96. Charles Duan, *Mandatory Infringement*, 75 FLA. L. REV. 219, 221, 227 (2018).

97. *Id.* at 221.

98. Sarah DeWeerdt, *The Environmental Concerns Driving Another Inhaler Makeover*, NATURE, May 14, 2020, at 14, 14.

99. *Id.* at 15. The fact that HFA inhalers were clinically effective at lower doses points to improved bioavailability in the lungs.

100. A. Cripps, M. Riebe, M. Schulze & R. Woodhouse, *Pharmaceutical Transition to Non-CFC Pressurized Metered Dose Inhalers*, 94 RESPIRATORY MED. 3, 3 (Supp. B, 2000).

101. *See id.* Notably, the authors were employees of Glaxo Wellcome, which manufactured brand-name versions of salbutamol (Ventolin) and fluticasone

Thus, the industry interpreted the need "to develop alternative propellants" as a convenient opportunity to extend market exclusivity of lucrative respiratory inhaler product lines while forcing generic and OTC competitors off the market.[102]

3. Results and future outlook: is an HFA switch next?

The CFC to HFA switch increased out-of-pocket costs and decreased utilization among asthma patients after the switch.[103] A separate study noted that "[o]ver the quarter-century since the first HFA-containing albuterol inhalers were approved, manufacturers have reaped immense financial rewards," pointing to approximately $14 billion in sales of "new" albuterol inhalers from 2007 to 2021.[104] In fact, albuterol inhalers experienced a substantial bump in revenues after the reformulation, largely due to restored market monopolies for these products.[105]

In its policy statement from September 2016, GlaxoSmithKline acknowledged that HFAs, while they do not deplete the ozone layer, "do have a relatively high [global warming potential] and as such they are included in the 1997 Kyoto Protocol on Climate Change which seeks to limit their release."[106] This seems to foreshadow a switch from

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propionate (Flixotide). *Id.* In 2000, Glaxo Wellcome PLC merged with SmithKline Beecham PLC to become GlaxoSmithKline PLC. *See* Alison Abbott, *Merger of Glaxo Wellcome and SmithKline Beecham Creates Pharmaceutical Giant*, 403 NATURE 232, 232 (2000).

102. *Id.*; s*ee* Wouters et al., *supra* note 92, at 1155 ("To be fair, brand name manufacturers did invest in research and development to bring their new HFA-based metered-dose inhalers to market; several companies claimed to have spent $250 million to $400 million to develop their products, though few details were provided. But the many billions of dollars in additional revenue earned by brand-name manufacturers over the past decade far exceeded these investments.").

103. *See* Anupam B. Jena, Oliver Ho, Dana P. Goldman & Pinar Karaca-Mandic, *The Impact of the US Food and Drug Administration Chlorofluorocarbon Ban on Out-of-Pocket Costs and Use of Albuterol Inhalers Among Individuals with Asthma*, 175 JAMA: INTERNAL MED. 1171, 1178 (2015) ("[T]he FDA ban on albuterol CFC inhalers was associated with large relative increases in out-of-pocket inhaler costs and slight declines in albuterol inhaler utilization among privately insured individuals with asthma."). Figure 1B in the Jena et al. article demonstrates trends in market utilization, in which HFA inhaler use after Q4 2008 represented almost all of the albuterol market through Q4 2010 (the end of data collection). *Id.* at 1175.

104. Wouters et al., *supra* note 92, at 1153.

105. *Id.* at 1153–54.

106. *GSK Public Policy Positions*, GSK 1, 3 (2016), https://us.gsk.com/media/2956/public-position-on-ozone-depletion-and-ancillary-plant-equipment-policy.pdf [https://perma.cc/MKK4-7PCM].

HFAs to a different propellant, potentially replicating the outcome from the CFC to HFA switch: barriers to patient access, excess spending, and exorbitant profits for manufacturers.

As Sarah DeWeerdt notes, "increasing attention . . . [is being paid to] the environmental impacts of . . . [HFA] propellants, which replaced CFCs but are themselves powerful greenhouse gases, . . . spurring innovations in inhaler design."[107] According to one study, one puff from an inhaler containing HFA-134a has "a global-warming potential equivalent to 0.13 kilograms of carbon dioxide."[108] As Wouters and colleagues note of albuterol inhalers:

> AstraZeneca and GlaxoSmithKline, two of the largest manufacturers of brand-name inhalers, are developing next-generation, low-carbon inhalers. Unless policymakers work to minimize the extent to which any new patents on these products delay the approval of generic equivalents, the United States may end up spending billions more in the coming decades on a product whose active ingredient was first approved in 1981.[109]

The arguments for the second round of reformulations are reminiscent of the CFC debate, when health officials and physicians raised concerns about access and patient care that could arise from a forced switch.[110] One potential alternative propellant is HFA-152a, which has a significantly smaller environmental impact as compared to HFA-134a.[111] Perhaps this was the plan all along: switch from CFCs to a propellant with less environmental impact (HFA-134a), then wait until environmentalists and other climate advocates demand a switch to an even "greener" propellant.[112]

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107. DeWeerdt, *supra* note 98, at 15.

108. *Id.* at 17.

109. Wouters et al., *supra* note 92, at 1155. In a separate article, Dr. Feldman and colleagues note that similar patent evergreening strategies are occurring in an adjacent therapeutic space, nebulizers (also indicated to treat respiratory conditions like asthma). *See* William B. Feldman, Doni Bloomfield, Reed F. Beall & Aaron S. Kesselheim, *Brand-Name Market Exclusivity for Nebulizer Therapy to Treat Asthma and COPD*, 40 NATURE BIOTECHNOLOGY 1319 (2022) (conducting a comparative study on patents for nebulizers and inhalers).

110. *See, e.g.*, DeWeerdt, *supra* note 98, at 17 (suggesting that medical professionals were concerned that a new formulation would negatively impact patients).

111. *Id.*

112. *See* Wouters et al., *supra* note 92, at 1155 (arguing that brand-name companies will financially benefit from these continued changes because of their interference with the generic approval process).

Others have advocated for a switch to dry powder inhalers ("DPIs") that do not rely on propellants for effective use. However, one study found that pMDIs were superior to DPIs in controlling symptoms of asthma, suggesting that they may not be the best replacement for pMDIs.[113] In a separate survey, patients preferred pMDIs over DPIs.[114] Some DPIs have taken advantage of this to product hop to HFA pMDIs. One prominent DPI, the Advair Diskus, switched formulations to an HFA before patents expired to extend market exclusivity, but, in the process, may have increased its carbon footprint.[115]

B. Case 2: Switch to Abuse-Deterrent Formulations of Opioids

One early article that set the tone for the use of opioids in treating chronic pain was a single paragraph published in the *New England Journal of Medicine* titled *Addiction Rare in Patients Treated with Narcotics*.[116] This brief study was used in multiple settings, including pharmaceutical promotion, to advance the belief that opioids were nonaddictive, which fueled a surge in use in the 1980s and 1990s driven by targeted pharmaceutical marketing campaigns.[117] Total prescribing reached a peak of 782 morphine milligram equivalents per

113. *See* Hae-Sim Park, Dukyong Yoon, Hyun Young Lee, Ga-Young Ban, Simon Wan Yau Ming & Joanna Ling Zhi Jie et al., *Real-Life Effectiveness of Inhaler Device Switch from Dry Powder Inhalers to Pressurized Metred-Dose Inhalers in Patients with Asthma Treated with ICS/LABA*, 24 RESPIROLOGY 972 (2019) ("Switching to and persisting with pMDI was associated with decreased asthma exacerbations and improved asthma control.").

114. Masato Muraki, Kyuya Gose, Soichiro Hanada, Hirochiyo Sawaguchi & Yuji Tohda, *Which Inhaled Corticosteroid and Long-Acting β-agonist Combination is Better in Patients with Moderate-to-Severe Asthma, a Dry Powder Inhaler or a Pressurized Metered-Dose Inhaler?*, 24 DRUG DELIVERY 1395, 1395 (2017).

115. *See* Sinha, *supra* note 14, at 319–21 (explaining how a change in Advair's formula for patent reasons ultimately undermined the company's stated environmental objectives).

116. *See generally* Jane Porter & Hershel Jick, *Addiction Rare in Patients Treated with Narcotics*, 302 NEW ENG. J. MED. 123 (1980) (noting that hospitalized medical patients seldom developed opioid addictions unless they already had a history of addiction).

117. *See* Jessica Bresler & Michael S. Sinha, *The Other Three Waves: Re-assessing the Impact of Industry-Prescriber Relations on the Opioid Crisis*, 41 J. LEG. MED. 47, 53–54 (2021) (finding that OxyContin's unsubstantiated claims regarding its nonaddictive quality drove sales for years).

capita in 2010.[118] Prescribing hit its highest point in 2012, with over 255 million prescriptions written for opioids in the United States.[119]

1. Emerging evidence for opioid misuse and overdose as a public health crisis

Eventually, it became clear that overprescribing of opioids did contribute to addiction. By then, pain was enshrined as the "fifth vital sign" and pain management was elevated in importance, perhaps too much so.[120] Eventually, increasing rates of opioid use disorder and overdose deaths put the issue on Congress' radar.[121]

In one prominent example, delayed-release OxyContin pills were marketed as twice-daily medications, lasting a full twelve-hours per dose.[122] Patients reported that the effects wore off after about eight hours, triggering a withdrawal process that was eventually relieved by a subsequent dose of OxyContin, fostering a physiologic dependence on the drug.[123] One physician was quoted in an *L.A. Times* exposé on the "twelve-hour problem" as saying, "[y]ou are messing with those areas of the brain that are involved in addiction, and you are going to get the person dependent on it."[124] Pill mills and physician shopping eventually drove the creation of numerous state-based prescription drug monitoring programs. These programs were initially designed to

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118. *Vital Signs: Changes in Opioid Prescribing in the United States, 2006–2015*, CTRS. FOR DISEASE CONTROL & PREVENTION (July 7, 2017) https://www.cdc.gov/mmwr/volumes/66/wr/mm6626a4.htm [https://perma.cc/NBV7-L7QJ].

119. *U.S. Opioid Dispensing Rate Maps*, CTRS. FOR DISEASE CONTROL & PREVENTION, https://www.cdc.gov/drugoverdose/rxrate-maps/index.html [https://perma.cc/6BAU-2T8Y] (last reviewed Nov. 10, 2021).

120. Richard. S. Davidson, Kendall Donaldson, Maggie Jeffries, Sumitra Khandelwal, Michael Raizman & Yasaira Rodriguez Torres et al., *Persistent Opioid Use in Cataract Surgery Pain Management and the Role of Nonopioid Alternatives*, 48 J. CATARACT REFRACTIVE SURGERY 730, 731 (2022). Though treatment of pain is important and many people with pain syndromes go untreated or undertreated, there are some more egregious instances of overprescribing. For one example, see *id.* for a discussion on opioid addiction and pain management in the context of cataract surgery.

121. *E.g.*, *id.* at 738 (noting the introductions of the 2018 Substance Use-Disorder Prevention that Promotes Opioid Recovery and Treatment for Patients and Communities (SUPPORT) Act and the Non-Opioids Prevent Addiction in the Nation (NO PAIN) Act).

122. U.S. Food & Drug Admin., Oxycontin Label: Highlights of Prescribing Information (revised Apr. 2010), https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/022272lbl.pdf [https://perma.cc/WV65-RLJ3].

123. Harriet Ryan, Lisa Girion & Scott Glover, *'You Want a Description of Hell?' OxyContin's 12-Hour Problem*, L.A. TIMES (May 5, 2016), https://www.latimes.com/projects/oxycontin-part1 [https://perma.cc/N2WS-7QDE].

124. *Id.*

track overprescribing by physicians and frequent receipt of prescriptions by patients but were later co-opted as a law enforcement tool.[125]

Once opioid prescribing was identified as a major culprit, public health authorities took a broad array of actions aimed at stemming the root causes of the pandemic. One of those was thought to be the excess prescribing of opioids and the diversion of those pills to the black market.[126] As a result, a law enforcement campaign, largely operated through the Drug Enforcement Administration (DEA), aimed to decrease supply by focusing attention on rogue prescribers and criminalizing the possession and trafficking of prescription opioids.[127]

2. Role of opioid manufacturers in the switch

The opioid crisis in the United States left policymakers clamoring for solutions that could decrease morbidity and mortality.[128] Amid the focus on diversion and misuse of prescription opioids, opioid manufacturers saw an opportunity.[129] With declining revenues on the

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125. *See* Jennifer D. Oliva, *Prescription-Drug Policing: The Right to Health-Information Privacy Pre- and Post-*Carpenter, 69 DUKE L.J. 775, 792–96 (2020) ("The fact that the majority of state [prescription drug monitoring programs] do not even require prescribers to query patient data proves that the databases are largely criminal and regulatory surveillance tools dressed up in public-health-promoting rhetoric."); *see also* Leo Beletsky, *Deploying Prescription Drug Monitoring to Address the Overdose Crisis: Ideology Meets Reality*, 15 IND. HEALTH L. REV. 139, 162–69 (2018) ("Broad law enforcement access to some of the most private health information creates a number of problems, including blurring the line between healthcare and law enforcement.").

126. Nabarun Dasgupta, Leo Beletsky & Daniel Ciccarone, *Opioid Crisis: No Easy Fix to Its Social & Economic Determinants*, 108 AM. J. PUB. HEALTH 182, 182–83 (2018); U.S. DEP'T OF JUST., REVIEW OF THE DRUG ENFORCEMENT ADMINISTRATION'S REGULATORY AND ENFORCEMENT EFFORTS TO CONTROL THE DIVERSION OF OPIOIDS 1–3 (Sept. 2019), https://oig.justice.gov/reports/2019/e1905.pdf [https://perma.cc/2QH2-68DG].

127. *See* Dasgupta et al., *supra* note 126, at 182–83; Brendan Saloner, Emma E. McGinty, Leo Beletsky, Ricky Bluthenthal, Chris Beyrer & Michael Botticelli et al., *A Public Health Strategy for the Opioid Crisis*, 133 PUB. HEALTH. REP. 24, 31 (Supp. 1 2018) (pointing out that federal statutes and criminal justice metrics are often utilized to undermine proliferation of controlled substances).

128. Ameet Sarpatwari, Michael S. Sinha & Aaron S. Kesselheim, *The Opioid Epidemic: Fixing a Broken Pharmaceutical Market*, 11 HARV. L. & POL'Y REV. 463, 463–64 (2017); *see also* Bresler & Sinha, *supra* note 117, at 69–70 (explaining that policymakers have issued guidelines and warnings to improve education surrounding overprescribing).

129. *See, e.g.*, Sarpatwari et al., *supra* note 128, at 474–75 (arguing that companies capitalized on the crisis to create a market for an alternative drug that was less addictive); Rachael P. McClure, *Generic Oxycontin®–Abuse Resistance Required Says FDA*,

horizon due to decreasing utilization and imminent generic entry, manufacturers began to pitch safer "abuse-deterrent" formulations of their opioid products to the FDA—new products with altered characteristics such that they would be less amenable to misuse and abuse by inhalation or injection.[130] Once new products with new regulatory and patent exclusivities were approved, brand manufacturers asserted that older products were less safe than the "abuse-deterrent" alternatives, thereby preventing generics from entering the space and securing an FDA-sanctioned hard switch for their product hop.[131]

Purdue Pharma led the charge. With market exclusivity for its blockbuster drug OxyContin slated to end in 2013, it modified the product's chemical composition to create an ADF of OxyContin.[132] By doing so, patent exclusivity was extended until 2030.[133] In order to mitigate misuse by inhalation or injection, the new product—reformulated to be harder to crush and to form a gel when mixed with

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FDA LAWS. BLOG (Apr. 22, 2013), http://www.fdalawyersblog.com/2013/04/generic-oxycontin-abuse-resis.html [https://perma.cc/R2QY-LJN4] (suggesting that Purdue's decision to create crush-proof tablets of their original OxyContin was motivated by their desire to maintain their patent).

130. *See* Sarpatwari et al., *supra* note 128, at 471 (describing Purdue Pharma's effort to restrict entry of generic extended-release oxycodone by securing patents for abuse-deterrent oxycodone); Jacob Sherkow, *Purdue Pharma & OxyContin: Regulatory Gamesmanship? A Debate*, STAN. L. SCH.: L. & BIOSCIENCES BLOG (May 5, 2013), https://law.stanford.edu/2013/05/05/lawandbiosciences-2013-05-05-purdue-pharma-oxycontin-regulatory-gamesmanship-a-debate [https://perma.cc/ZF3Z-SW2C] (arguing that pharmaceutical companies made changes to existing products that made them "safer" in an effort to keep their patents and because of the threat of profit loss due to the expansion of generics).

131. Sarpatwari et al., *supra* note 128, at 471–72; *see* Nancy Shute & Audrey Carlsen, *FDA's Rejection Of Generic OxyContin May Have Side Effects*, NPR (Apr. 18, 2013, 11:41 AM), https://www.npr.org/sections/health-shots/2013/04/17/177602393/why-fdas-rejection-generic-oxycontin-may-have-side-effects [https://perma.cc/XBL2-EL3U] (reporting that "the FDA said that it won't approve generic versions of the original formulation of OxyContin, a long-acting narcotic pain medication, which went off patent that day").

132. *See* Katherine Ellen Foley, *Big Pharma is Taking Advantage of Patent Law to Keep OxyContin from Ever Dying*, QUARTZ (Nov. 18, 2017), https://qz.com/1125690/big-pharma-is-taking-advantage-of-patent-law-to-keep-oxycontin-from-ever-dying [https://perma.cc/3QY8-MJGW] ("Purdue has been able to file new patents for OxyContin [thirteen] times with the [U.S.] Patent and Trademark Office over the past decade, thereby extending its exclusive selling rights on the drug through 2030.").

133. *Id.*

water—produced an abrupt decline in misuse of OxyContin pills.[134] However, many individuals switched to other opioids available on the black market, including heroin.[135] After early evidence pointed to decreases in OxyContin misuse coinciding with increases in heroin misuse,[136] one study was able to correlate pre-switch OxyContin misuse with post-switch heroin mortality.[137] Despite growing concerns about ADFs,[138] other companies followed suit in producing similar compounds.[139]

Pharmaceutical manufacturers quickly got the FDA on board:

> The FDA is encouraging the development of prescription opioids with . . . [ADFs] to help combat the opioid crisis . . . . The FDA is working with many drug makers to support advancements in this area and helping drug makers navigate the regulatory path to market as quickly as possible. In working with industry, the FDA is

134. Theodore J. Cicero & Matthew S. Ellis, *Abuse-Deterrent Formulations and the Prescription Opioid Abuse Epidemic in the United States: Lessons Learned from OxyContin*, 72 JAMA: PSYCHIATRY 424, 427 (2015) (Figure 1).

135. *See* William N. Evans, Ethan Lieber & Patrick Power, *How the Reformulation of OxyContin Ignited the Heroin Epidemic* 1, 7 (Nat'l Bureau of Econ. Rsch.: Working Paper No. 24475, 2018), https://www.nber.org/system/files/working_papers/w24475/w24475.pdf [https://perma.cc/N2EJ-BZVK] (noting that heroin was a cheaper and more readily available alternative to prescription opioids).

136. *See* Theodore J. Cicero, Matthew S. Ellis & Hilary L. Suratt, *Effect of Abuse-Deterrent Formulation of OxyContin*, 367 NEW ENG. J. MED. 187, 188–89 (2012) ("OxyContin fell from 47.4% of respondents to 30.0% . . . , whereas heroin use nearly doubled.").

137. Abby Alpert, David Powell & Rosalie Liccardo Pacula, *Supply-Side Drug Policy in the Presence of Substitutes: Evidence from the Introduction of Abuse-Deterrent Opioids*, 10 AM. ECON. J.: ECON. POL'Y 1, 24 (2018); *see also* Evans et al., *supra* note 135, at 1–2, 4 (explaining that the abuse-deterrent formulation of OxyContin undermined the likelihood of the opioid's abuse, leading many to abuse and fatally overdose on heroin).

138. *See* Gregory D. Curfman, Leo Beletsky & Ameet Sarpatwari, *Benefits, Limitations, and Value of Abuse-Deterrent Opioids*, 178 JAMA: INTERNAL MED. 131, 131–32 (2018) (writing that while "[s]elective use of AD opioids may be effective in mitigating opioid abuse and reducing drug diversion. . . . their widespread use . . . may have the unintended consequence of promoting switching to more dangerous opioids").

139. Letter to John F. Weet, Vice President of Reg. Affs. at Collegium Pharm. Inc. from Judith A. Racoosin, Deputy Dir. of Safety in the Div. of Anesthesia, Analgesia, and Addiction Prods. at FDA (May 26, 2017) (on file with the FDA), https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2017/208090Orig1s006ltr.pdf [https://perma.cc/4BR9-S2RP] (approving an updated Risk Evaluation and Mitigation Strategy for XTAMPZA ER, an ADF of oxycodone produced by Collegium Pharmaceutical Inc.).

> taking a flexible, adaptive approach to the evaluation and labeling of potentially abuse-deterrent products.[140]

While acknowledging the limitations of ADF technology, the FDA nonetheless "continue[s] to encourage the development of innovative abuse-deterrent technologies," each of which also happen to come with patent protection and new market exclusivity terms.[141]

3. Result: limited uptake of ADFs

Despite the initial praise and promise, the ADF market did not take off as intended. First, they provide little added therapeutic value to patients who take opioids chronically.[142] ADFs may provide less diversion value, but they provide no additional benefit over their predecessors when taken as prescribed.[143] Second, the products are often cost-prohibitive, which means that their potential benefits in certain individuals are far outweighed by cost.[144] The Institute for Clinical and Economic Review noted in its report on the effectiveness and value of ADFs that use of ADFs could prevent some cases of misuse,

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140. *Abuse-Deterrent Opioid Analgesics*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/abuse-deterrent-opioid-analgesics [https://perma.cc/8K3W-4QG8] (last updated Mar. 8, 2021).

141. *Id.*

142. INST. FOR CLINICAL & ECON. REV., ABUSE-DETERRENT FORMULATIONS OF OPIOIDS: EFFECTIVENESS AND VALUE 45 (2017), http://icerorg.wpengine.com/wp-content/uploads/2020/10/NECEPAC_ADF_Final_Report_08_08_17.pdf [https://perma.cc/U73K-36WB] ("For patients being considered for an opioid for therapeutic purposes, we judge the comparative clinical effectiveness of OxyContin to be 'C+' for the risk of abuse . . . ."); *see* Tien M. Nguyen, *Abuse-Deterrent Opioids: Worth the Cost and Effort?*, C&EN (Nov. 23, 2017) https://pubs.acs.org/doi/10.1021/cen-09545-cover2 [https://perma.cc/TX4P-QU58] (suggesting that the increased cost of ADFs cuts off access for people who need opioids and negatively impacts pain management treatment).

143. INST. FOR CLINICAL & ECON. REV., *supra* note 142, at 45 ("ADFs and their non-ADF counterparts are bioequivalent, producing the same analgesic benefits, and have the same profile of adverse effects when used as prescribed.").

144. *Id.* at 69 ("Our economic modeling analyses indicate that ADF opioids have the potential to substantially reduce the incidence of abuse in opioid-prescribed chronic pain patients relative to non-ADF opioids, but at significantly higher costs to the health care system. Even when important societal costs are included, ADF opioids were still estimated to increase overall costs.").

but at a significant cost.[145] Among patients in Medicare Part D, there was a modest and declining uptake of ADFs from 2015–2018.[146]

C. Case 3: OTC Naloxone

Naloxone, a drug used to reverse the effects of opioids, was developed in 1966, approved by the FDA in 1971, and upon approval, used exclusively by clinicians in hospital settings.[147] Even as generic injectable forms of the drug were developed, they remained limited to inpatient use for the controlled reversal of opioid-induced sedation.[148] In response to rising rates of opioid overdose in public settings, naloxone assembly kits that included prefilled syringes of naloxone and nasal atomizers were modified for intranasal delivery of the drug in non-clinical settings, though some assembly was required.[149] The FDA did not approve the kit before release and recalled the nasal atomizer over concerns that it sprayed a stream of the drug into the person's nose rather than the intended mist.[150] Developed with considerable federal support, the FDA approved an intranasal naloxone device in 2015 that required no assembly, manufactured by Adapt Pharma and sold as Narcan.[151] Despite the presence of intranasal

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145. *Id.* at 68.

146. U.S. FOOD & DRUG ADMIN., REPORT ON ABUSE-DETERRENT OPIOID FORMULATIONS AND ACCESS BARRIERS UNDER MEDICARE 6 (2020).

147. *See* Sinha, *supra* note 14, at 345–53 (discussing the role of device patents on delayed entry of generic forms of intranasal naloxone products, focusing on federal contributions to the development of a new formulation of the opioid overdose rescue drug).

148. Sinha, *supra* note 14, at 345; Ravi Gupta, Nilay D. Shah & Joseph S. Ross, *The Rising Price of Naloxone—Risks to Efforts to Stem Overdose Deaths*, 375 NEW ENG. J. MED. 2213, 2214 (2016).

149. *See, e.g.*, Kathryn G. Tippey, Mary Yovanoff, Larry S. McGrath & Peter Sneeringer, *Comparative Human Factors Evaluation of Two Nasal Naloxone Administration Devices: NARCAN® Nasal Spray and Naloxone Prefilled Syringe with Nasal Atomizer*, 8 PAIN & THERAPY 89, 92 (2019). Figure 4 is an example of Naloxone use instructions. *Id.* at 92 fig.4.

150. Nadia Kounang, *Recall Issued for Device that Delivers Overdose Reversal Drug*, CNN: HEALTH (Nov. 4, 2016, 6:20 PM), https://www.cnn.com/2016/11/04/health/naloxone-atomizer-recall/index.html [https://perma.cc/BL5M-2RF7].

151. Varun Saxena, *Narcan® (Naloxone Hydrochloride) Nasal Spray Approved by U.S. Food and Drug Administration*, FIERCE PHARMA (Nov. 23, 2015, 1:01 PM), https://www.fiercepharma.com/drug-delivery/narcan%C2%AE-naloxone-hydrochloride-nasal-spray-approved-by-u-s-food-and-drug [https://perma.cc/N7U4-W9FW]. Narcan was also the brand-name of the initial injectable formulation of the drug.

Narcan on the market when the nasal atomizer recall occurred, excess demand led to shortages.[152]

1. Intranasal Naloxone and the opioid crisis

Given the importance of intranasal naloxone as a harm reduction tool in the worsening opioid crisis, advocates pushed for greater availability of the drug.[153] Community groups have been integral in the purchase and distribution of naloxone in areas with high rates of overdose.[154] Some groups recommended expanded access to the drug in community pharmacies, including standing orders that allowed access without a prescription.[155]

Effectively, the federal government paid the manufacturer to develop its product hopped intranasal formulation. Other products, like an injectable naloxone delivery device (Evzio, made by Kaleo) also entered the market. *See* Sinha, *supra* note 14, at 347–48 (stating that Narcan was developed by a researcher who received $3.45 million in federal funding).

152. *See* Tessema et al., *supra* note 22, at 1029–32 (explaining several reasons why drug shortages occur, such as from manufacturing issues, as well as their impact on the market and prices).

153. *See* Corey S. Davis & Derek Carr, *Legal Changes to Increase Access to Naloxone for Opioid Overdose Reversal in the United States*, 157 DRUG & ALCOHOL DEPENDENCE 112, 113–17 (2015) [hereinafter Davis & Carr, *Increase Access*] (discussing policies such as naloxone access laws, third party prescribing, standing orders for naloxone distribution, expanded access through pharmacies, immunity provisions for providers, and Good Samaritan laws).

154. *See* Angela K. Clark, Christine M. Wilder & Erin L. Winstanley, *A Systematic Review of Community Opioid Overdose Prevention and Naloxone Distribution Programs*, 8 J. ADDICTION MED. 153, 153 (2014) (noting 188 community-run programs operating in the United States at the time).

155. Traci C. Green, Emily F. Dauria, Jeffrey Bratberg, Corey S. Davis & Alexander Y. Walley, *Orienting Patients to Greater Opioid Safety: Models of Community Pharmacy-based Naloxone*, 12 HARM REDUCTION J. 25, 27 (2015); *see also* Avik Chatterjee, Shapei Yan, Ziming Xuan, Katherine M. Waye, Audrey M. Lambert & Traci C. Green et al., *Broadening Access to Naloxone: Community Predictors of Standing Order Naloxone Distribution in Massachusetts*, DRUG & ALCOHOL DEPENDENCE Jan. 1, 2022, at 1, 2 (2022) ("Pharmacy standing orders, which allow dispensing of a medication or treatment without an individual prescription, have historically been a strategy used to improve access to and uptake of important public health interventions.").

2. The push for OTC intranasal naloxone

Despite these incremental advancements in increasing the availability of naloxone, many advocates believed it was not enough.[156] Corey S. Davis and Derek Carr noted that "[a]lthough states and the [FDA] have acted to increase access to naloxone, these changes are insufficient to address this unprecedented crisis."[157] Noting limited federal activity in the area, Davis and Carr called for naloxone to be reclassified as OTC.[158]

As momentum for a switch to OTC increased, the manufacturer showed little interest in initiating the switch on its own. In January 2019, FDA Commissioner Scott Gottlieb announced "unprecedented new efforts" to make naloxone available OTC.[159] The FDA approved the first generic version of intranasal naloxone in April 2019.[160] After an initial assessment of the issue in November 2022, an FDA Advisory Committee unanimously recommended on February 15, 2023 that naloxone be made available OTC without a prescription.[161] Two manufacturers applied for nonprescription status, with the FDA

156. *See* Corey S. Davis & Derek Carr, *Over the Counter Naloxone Needed to Save Lives in the United States*, 130 PREVENTIVE MED. 105932, 1–2 (2020) [hereinafter Davis & Carr, *Naloxone Needed*] (arguing that "naloxone's continued status as a prescription medication creates more harm than it prevents, contributing directly to this lifesaving medication often being unavailable when and where it is most needed").

157. *Id.* at 1.

158. *Id.* at 2 ("Despite the filing of several citizen petitions, FDA has failed to modify naloxone's prescription status, and manufacturers have neither requested nor appear likely to request that FDA switch an existing product from prescription-only to OTC.").

159. *Statement from FDA Commissioner Scott Gottlieb, M.D., on Unprecedented New Efforts to Support Development of Over-the-Counter Naloxone to Help Reduce Opioid Overdose Deaths*, U.S. FOOD & DRUG ADMIN. (Jan. 17, 2019), https://www.fda.gov/news-events/press-announcements/statement-fda-commissioner-scott-gottlieb-md-unprecedented-new-efforts-support-development-over [https://perma.cc/FL74-F8RJ].

160. News Release, U.S. Food & Drug Admin., FDA Approves First Generic Naloxone Nasal Spray to Treat Opioid Overdose (Apr. 19, 2019), https://www.fda.gov/news-events/press-announcements/fda-approves-first-generic-naloxone-nasal-spray-treat-opioid-overdose [https://perma.cc/MN47-7697].

161. Lev Facher, *FDA Advisers Recommend Approval of Over-the-Counter Naloxone to Fight Opioid Overdose*, STAT NEWS (Feb. 15, 2023), https://www.statnews.com/2023/02/15/naloxone-otc-opioisa-fda-panel-recommends [https://perma.cc/9LAH-K7QS]; *see also* News Release, U.S. Food & Drug Admin., FDA Announces Preliminary Assessment that Certain Naloxone Products Have the Potential to be Safe and Effective for Over-the-Counter Use (Nov. 15, 2022), https://www.fda.gov/news-events/press-announcements/fda-announces-preliminary-assessment-certain-naloxone-products-have-potential-be-safe-and-effective [https://perma.cc/R4EU-6WQ9] (explaining that the agency remains dedicated to reducing death by opioid overdose).

approving those applications in March 2023 and July 2023, respectively.[162]

Though this development is promising, other factors remain important for meaningful access, including low-cost generic alternatives and increased supply. Given that the current retail cost of Narcan is between $35 and $65, the product may in fact be less accessible due to cost even when it is more readily available on a pharmacy shelf.[163] With only two generic alternatives available as of writing this Article, prices may not fall significantly in the early period.[164]

3. Missed opportunities to optimize public health benefit

Given the drug's safety profile and proven track record of saving lives, increased access to the drug should have occurred sooner.[165] Two distinct time points are relevant here. First, at the time intranasal Narcan was approved in November 2015, a more modest incentive structure could have allowed for earlier generic competition. Second, the OTC switch could have happened soon after Commissioner Gottlieb's announcement in 2019 rather than four years later. The incremental increases in pharmacy access prior to the OTC switch led to only moderate improvements in access amid a worsening crisis.[166] Each of these moves—from intravenous to intranasal and from prescription to OTC—constitute product hops.

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162. Facher, *supra* note 161; *see also* News Release, U.S. Food & Drug Admin., FDA Approves First Over-the-Counter Naloxone Nasal Spray (Mar. 29, 2023), https://www.fda.gov/news-events/press-announcements/fda-approves-first-over-counter-naloxone-nasal-spray [https://perma.cc/26VD-7JRZ]; News Release, U.S. Food & Drug Admin., FDA Approves Second Over-the-Counter Naloxone Nasal Spray Product, (July 28, 2023), https://www.fda.gov/news-events/press-announcements/fda-approves-second-over-counter-naloxone-nasal-spray-product [https://perma.cc/PCZ6-8NHL].

163. Facher, *supra* note 161.

164. Indeed, generic entry has the most substantial impact on drug costs when there are four or more generic competitors. *See* Tessema et al., *supra* note 22, at 1024–26 (discussing the role of "niche drug markets" with three or fewer competitors in preserving high prices, even among off-patent drugs).

165. *See generally* Davis & Carr, *Increase Access*, *supra* note 153, at 1–2 (discussing the fact that most drug overdoses occur outside of a formal healthcare setting and explaining how programs to make naloxone publicly available assist in decreasing overdoses).

166. *See generally* Davis & Carr, *Naloxone Needed*, *supra* note 153, at 113 (explaining that provider hesitancy and the requirement of a prescription ensured pharmacy access did not provide significant improvements).

Moreover, some policy advocates have noted that the OTC switch for naloxone is necessary but not sufficient to address the crisis, emphasizing the need to increase public health interventions focused on harm reduction and increased supply and distribution.[167] Naloxone also remains cost-prohibitive at a launch price of $50 per carton of two at retail pharmacies.[168] Given the immense public health value of the naloxone OTC switch, incentives might have to be conditioned on reasonable pricing or availability of generic alternatives to ensure appropriate utilization.

III. INCENTIVIZING PUBLIC HEALTH PRODUCT HOPS

The challenge inherent to public health product hops is that the FDA historically has not given much weight to public health considerations when approving new products.[169] When such considerations are raised, these case examples suggest that they are raised by manufacturers themselves and may come with ulterior

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167. *See generally* John C. Messinger, Leo Beletsky, Aaron S. Kesselheim & Rachel E. Barenie, *Moving Naloxone Over the Counter Is Necessary but Not Sufficient*, 176 ANNALS INTERNAL MED. 1109, 1109 (2023) ("We must also continue to prioritize comprehensive methods of distribution, such as overdose education and naloxone distribution programs, that serve as important tools to reach the most vulnerable populations. In addition, simultaneous investment in harm-reduction strategies, such as supervised consumption spaces, is critical to ensure that naloxone is available in settings where its life-saving potential can be most fully realized.").

168. Bhanvi Satija, *Emergent Aims to Price Over-the-Counter Narcan at About $50*, REUTERS (Apr. 20, 2023, 11:56 AM), https://www.reuters.com/business/healthcare-pharmaceuticals/emergent-aims-price-over-the-counter-narcan-about-50-2023-04-20 [https://perma.cc/SL5H-Y9FU].

169. Observers also noted the FDA's disregard for public health considerations when it continued to approve potent opioids amid a worsening public health crisis, even products that did not purport to be ADFs. *See, e.g.*, Debra Goldschmidt, *Amid Deepening Addiction Crisis, FDA Approves Powerful New Opioid*, CNN: HEALTH, https://www.cnn.com/2018/11/02/health/new-opioid-dsuvia-fda-approval-bn/index.html [https://perma.cc/9FVU-PPGV] (last updated Nov. 4, 2018, 9:16 AM) (stating that the FDA approved a drug five to ten times more powerful than fentanyl); *see also* NAT'L ACADS. OF SCIS., ENG'G & MED. COMM. ON PAIN MGMT. & REGUL. STRATEGIES TO ADDRESS PRESCRIPTION OPIOID ABUSE, PAIN MANAGEMENT AND THE OPIOID EPIDEMIC: BALANCING SOCIETAL AND INDIVIDUAL BENEFITS AND RISKS OF PRESCRIPTION OPIOID USE 9 (2017) ("The [FDA] should commit to increasing the transparency of its regulatory decisions for opioids to better inform manufacturers and the public about optimal incorporation of public health considerations into the clinical development and use of opioid products.").

motives to extend market exclusivity, preserve monopolies, and raise costs.[170]

In light of this, Congress should curtail incentives for product hops, except for those that stand to offer real (not perceived) public health benefit. Here I review some existing incentive programs in pharmaceutical policy, propose some alternatives, and chart a path forward.

A. Existing Incentive Structures

There are a number of existing incentives—push and pull—to persuade pharmaceutical manufacturers to pursue certain areas of research and development.[171] Some have been more impactful, where others have not stimulated research and development in meaningful ways.[172] Yet, when it comes to pharmaceutical incentives, Congress seems to prefer incentives that do not require additional funding, despite evidence that unfunded incentives are either not very effective or have excessive indirect costs.[173]

1. Patent extensions

Pediatric research and development for a given therapeutic is often delayed until after approval—if it is completed at all.[174] In an effort to

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170. Jacob Sherkow, *Purdue Pharma & OxyContin: Regulatory Gamesmanship? A Debate*, STAN. L. SCH.: L. & BIOSCIENCES BLOG (May 5, 2013), https://law.stanford.edu/2013/05/05/lawandbiosciences-2013-05-05-purdue-pharma-oxycontin-regulatory-gamesmanship-a-debate [https://perma.cc/RWM7-6UZP]; McClure, *supra* note 129.

171. Push incentives are those that "push" a desirable product closer to market, usually by direct financial outlays from federal funding sources. In contrast, pull incentives are rewards intended to be alluring enough to "pull" a manufacturer toward FDA approval and marketing of a desirable product. *See* INST. OF MED. OF THE NAT'L ACADS., THE PUBLIC HEALTH EMERGENCY MEDICAL COUNTERMEASURES ENTERPRISE: INNOVATIVE STRATEGIES TO ENHANCE PRODUCTS FROM DISCOVERY THROUGH APPROVAL 38, 40 (2010) (listing common push and pull incentives).

172. *See* Kevin J. Kraushaar, *Market Exclusivity After a Prescription to Nonprescription Drug Switch: Striking the Right Balance Between Innovation and Competition*, 54 FOOD & DRUG L.J. 243, 243 (1999) (detailing the effect that modern developments have had on the application process for an OTC switch and how the "clinical studies" standard from 1984 has drastically changed).

173. *See infra* Sections III.A.1–3.

174. Alyson Karesh, Presentation on Pediatric Drug Development: Regulatory Expectations (2015), https://www.fda.gov/files/drugs/published/Pediatric-Drug-Development–Regulatory-Expectations.pdf [https://perma.cc/C7Z2-252H] (slide 27) ("The submission of some or all assessments may be *deferred* until a specified date after approval.").

reward manufacturers for conducting research in pediatric populations and generating data—positive or negative—about safety and efficacy in children, Congress first established the pediatric exclusivity program in 1997, later integrated into the Best Pharmaceuticals for Children Act of 2002[175] ("BPCA").[176] Manufacturers that propose and complete studies of their products in children receive six months of patent extension on all patents in the product portfolio regardless of the outcome of the study (positive or negative).[177] In order to qualify for the exclusivity, a Written Request must be issued by the FDA, either on its own accord or, more commonly, at the request of a pharmaceutical manufacturer.[178]

Several studies have identified that even a six-month exclusivity extension can provide outsized rewards for manufacturers well beyond the costs of pediatric studies.[179] Those rewards have become larger over time, raising questions among policymakers as to whether the program should continue.[180] Opponents of the BPCA note that the Pediatric Research Equity Act[181] ("PREA") already mandates such studies and

175. Best Pharmaceuticals for Children Act of 2002, Pub. L. 107-109, 115 Stat. 1408 (codified as amended in scattered sections of 21 U.S.C. & 42 U.S.C.).

176. *See* Florence T. Bourgeois & Aaron S. Kesselheim, *Promoting Pediatric Drug Research and Labeling—Outcomes of Legislation*, 381 NEW ENG. J. MED. 875, 875 (2019) (explaining that the FDA can formally request additional studies, for which companies performing those studies would receive six extra months of patent exclusivity); *see also* Michael S. Sinha, Mehdi Najafzadeh, Elizabeth K. Rajasingh, James Love & Aaron S. Kesselheim, *Labeling Changes and Costs for Clinical Trials Performed Under the US Food and Drug Administration Pediatric Exclusivity Extension, 2007 to 2012*, 178 JAMA: INTERNAL MED. 1458, 1459 (2018) (explaining that historically few prescription drugs were tested on children before being used by children).

177. *See* 21 U.S.C. § 355a(b)(1) (explaining the process through which a pediatric study can begin to test a new pediatric drug).

178. *See id.* § 355a(d)(1)(A).

179. *See* Jennifer S. Li, Eric L. Eisenstein, Henry G. Grabowski, Elizabeth D. Reid, Barry Mangum & Kevin A. Schulman et al., *Economic Return of Clinical Trials Performed Under the Pediatric Exclusivity Program*, 297 JAMA 480, 485–87 (2007) (detailing how pharmaceutical products with over one billion dollars in sales see a higher return than those with smaller annual revenues); *see also* Sinha et al., *supra* note 176, at 1464 (concluding that the pediatric exclusivity extension produces pediatric indications for several drugs while also providing substantial rewards to drug manufacturers).

180. *See* Joshua M. Sharfstein, *Reform at the FDA—In Need of Reform*, 323 JAMA 123, 124 (2020) (estimating that pediatric trials "cost the health care system more than $6 for every $1 spent by a company on a pediatric trial").

181. Pediatric Research Equity Act of 2003, 21 U.S.C. § 335c.

effectively generates new data on research in children.[182] The National Institutes of Health also conducts research on the use of older, off-patent medicines in children through its Pediatric Trials Network.[183]

Yet in the context of public health product hops, a six-month patent exclusivity extension could provide a significantly less outsized reward for research and development as compared to the current process of approving a new drug application with its accompanying patent and regulatory exclusivities. As long as new products are phased in and old ones phased out over time via a soft switch, a six-month exclusivity period could be justifiable, particularly if substantial public health benefit results.

2. Priority review vouchers

In an effort to stimulate research and development into neglected tropical diseases, Congress in 2007 created a priority review voucher ("PRV") program. Under the program, manufacturers that marketed new treatments for one of the listed neglected tropical diseases could receive PRVs.[184] The manufacturer could choose to redeem a PRV to accelerate FDA review of a different application (from ten months to six months) or to sell the PRV. The program has since been expanded to include rare pediatric diseases and medical countermeasures.[185]

Multiple studies have shown that PRVs have not resulted in increases in research and development. For neglected tropical diseases, the introduction of the PRV program did not lead to an increase in the initiation of Phase I clinical trials for drugs treating the listed

182. *See* Bourgeois & Kesselheim, *supra* note 176, at 877–78 ("The intent of the rule was to ensure that for all new drugs, data on safety and efficacy in children were included, as well as information on dosing and administration in relevant pediatric populations.").

183. *Our Research*, PEDIATRIC TRIALS NETWORK, https://pediatrictrials.org/our-research [https://perma.cc/ZPP9-JRA2].

184. *See* David B. Ridley, Henry G. Grabowski & Jeffrey L. Moe, *Developing Drugs for Developing Countries*, 25 HEALTH AFFS. 313, 313–14 (2006) (outlining what this type of program should look like and the history of the PRV program more generally); *see also* David B. Ridley, Pranav Ganapathy & Hannah E. Kettler, *US Tropical Disease Priority Review Vouchers: Lessons in Promoting Drug Development and Access*, 40 HEALTH AFFS. 1243, 1243–44 (2021) (reporting that "[a]s of the end of 2020 the FDA had awarded forty-four vouchers: twelve for tropical diseases, twenty-eight for rare pediatric diseases, and four for medical countermeasures").

185. Ridley et al., *supra* note 184, at 1244.

conditions.[186] Similarly, rare pediatric diseases research was not stimulated as a result of the program.[187] For medical countermeasures, the program incentivized research and development that was already underway, much of it in federal government agencies like Biomedical Advanced Research and Development Authority and Defense Advanced Research Projects Agency (both within the Department of Defense) that do not stand to benefit from PRVs.[188]

PRVs have been lucrative assets for manufacturers and have sold for prices as high as $350 million.[189] However, their value is likely to diminish over time as more PRVs are issued.[190] Importantly, PRVs are an unfunded mandate—the FDA must review products on an accelerated timeline but is not allocated additional resources to do so.[191] Risk of post-market safety issues increases in products that are approved close to regulatory deadlines.[192] In spite of these concerns, Congress is unlikely to repeal PRVs or allow them to sunset, though it

186. Nina Jain, Thomas Hwang, Jessica M. Franklin & Aaron S. Kesselheim, *Association of the Priority Review Voucher with Neglected Tropical Disease Drug and Vaccine Development*, 318 JAMA 388, 388 (2017) (revealing that the number of neglected tropical disease drugs between 2000 and 2007 was thirty-two and the number only increased to thirty-four between 2008 and 2014).

187. Thomas J. Hwang, Florence T. Bourgeois, Jessica M. Franklin & Aaron S. Kesselheim, *Impact of the Priority Review Voucher Program on Drug Development for Rare Pediatric Diseases*, 38 HEALTH AFFS. 313, 318 (2019) (showing a greater likelihood that drugs would advance from Phase I to Phase II but showing no significant changes in later stages of development).

188. Michael S. Sinha, Nina Jain, Thomas J. Hwang & Aaron S. Kesselheim, *Expansion of the Priority Review Voucher Program Under the 21st Century Cures Act: Implications for Innovation and Public Health*, 44 AM. J.L. & MED. 329, 337 (2018) (explaining that both Agencies "are important sources of funding for the discovery, development, and procurement of medical countermeasure products").

189. *E.g.*, Reuters Staff, *AbbVie Buys Special Review Voucher for $350 Million*, REUTERS (Aug. 19, 2015, 10:47 AM), https://www.reuters.com/article/us-abbvie-priorityreview/abbvie-buys-special-review-voucher-for-350-million-idUSKCN0QO1LQ20150819 [https://perma.cc/CUT2-6YCY] (reporting that AbbVie Inc. purchased a $350 million PRV to accelerate the review process for one of its drugs).

190. *See* Sinha et al., *supra* note 188, at 339 (discussing how multiple vouchers being available on the market at the same time decreases the vouchers' value).

191. *Id.* at 335.

192. Sana R. Mostaghim, Joshua J. Gagne & Aaron S. Kesselheim, *Safety Related Label Changes for New Drugs After Approval in the US Through Expedited Regulatory Pathways: Retrospective Cohort Study*, 358 BRIT. MED. J., Aug. 2, 2017, at 1, 1.

has held Congressional hearings on the value of these programs in the past.[193]

Offering PRVs for public health product hops may be problematic for the same reasons that make the current program ineffectual: (1) their value diminishes over time, making them less lucrative to manufacturers looking to reformulate products;[194] (2) they accelerate review of other products, placing additional strain on limited FDA resources;[195] and (3) they may incentivize manufacturers to make incremental changes to obtain PRVs, even if those changes do not truly advance public health objectives.[196]

3. Expedited approval

In the examples discussed above, manufacturers have been given a window of time to reformulate products while phasing out products that have been shown to cause or contribute to public health harm. That said, expediting their market launch via various regulatory incentive programs (accelerated approval, breakthrough designation, fast track) may be problematic. To its advantage, it may offset time and costs in mandated product switches including phasing out CFCs from pMDIs. However, it can also create a situation in which the fastest movers enter the market sooner. This establishes periods of market monopoly that result in higher market prices for new products while dramatically increasing costs to consumers. It may be preferable for market competition if old products do not exit the market until several new products are available to consumers, especially if the benefits are to public health rather than to individual patients. This is what Congress intended with the switch from CFCs; a phase-out of older products only when sufficient alternatives existed, such that patient access would not be meaningfully disrupted.[197]

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193. *See Improving Access to Care: Legislation to Reauthorize Key Public Health Programs, Hearing on H.R. 4439 Before the Subcomm. on Health of the H. Comm. on Energy & Com.*, 116th Cong. (2020) (statement of Aaron S. Kesselheim).

194. *See* Sinha et al., *supra* note 188, at 339 (asserting the value of PRVs decreases over time for multiple reasons including availability of numerous vouchers and the lack of difference of standard and priority review times).

195. *Id.* at 335.

196. *See id.* at 339–40 (finding vouchers have been awarded for products that required no innovative research).

197. McAllister, *supra* note 88.

4. Restoration of market exclusivity

Another program that allowed manufacturers to restore market exclusivity for their products was the now-defunct Unapproved Drugs Initiative, which awarded three years of market exclusivity for any manufacturer to study the efficacy of older, off-patent drugs.[198] The FDA designed the pathway in order to incentivize the generation of more data for older drugs that had not previously been approved by the agency.[199] Eventually, it became clear that the de facto market exclusivity award "allowed manufacturers an opportunity to raise prices in an environment largely insulated from market competition."[200]

As of 2015, thirty-four products went through the Unapproved Drugs Initiative.[201] Applications for many of the products did not generate new data from clinical trials, but rather from literature reviews of existing studies.[202] The consequences of restoring market monopolies were predictable yet harmful: shortages, increased prices, and disrupted patient access to affordable generic drugs.[203] In one case, studies of colchicine led to three years of market exclusivity for

198. *See* Simon Gunter, Aaron S. Kesselheim & Benjamin N. Rome, *Market Exclusivity and Changes in Competition and Prices Associated with the US Food and Drug Administration Unapproved Drug Initiative*, 181 JAMA: INTERNAL MED. 8 (2021), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8129902 [https://perma.cc/WWM4-STCB] (reporting that the majority of Unapproved Drugs Initiative approvals from March 2008 to October 2017 had an actual market exclusivity period of three years or longer); Termination of the Food and Drug Administration's Unapproved Drugs Initiative; Request for Information Regarding Drugs Potentially Generally Recognized as Safe and Effective; Withdrawal, 86 Fed. Reg. 28, 605 (May 27, 2021) (effectively terminating the Unapproved Drugs Initiative).

199. DEP'T OF HEALTH & HUM. SERV., FREQUENTLY ASKED QUESTIONS REGARDING THE DEPARTMENT OF HEALTH AND HUMAN SERVICES' ANNOUNCEMENT ON THE UNAPPROVED DRUGS INITIATIVE, https://www.hhs.gov/sites/default/files/covid-19-unapproved-drugs-initiative.pdf [https://perma.cc/AZS5-H9PH].

200. *Id.*

201. Ravi Gupta, Sanket S. Dhruva, Erin R. Fox & Joseph S. Ross, *The FDA Unapproved Drugs Initiative: An Observational Study of the Consequences for Drug Prices and Shortages in the United States*, 23 J. MANAGED CARE & SPECIALTY PHARMACY 1066, 1067 (2017).

202. *See id.* at 1069, 1073 (utilizing literature reviews for eleven out of nineteen drugs).

203. *See id.* at 1072–73 (identifying price increases and access shortages as consequences of the Unapproved Drugs Initiative).

brand-name Colcrys.[204] Generic colchicine tablets, which cost 9¢ a pill at the time, were forced off the market, replaced by Colcrys tablets selling for $4.85 a pill.[205]

Though not done through the Unapproved Drugs Initiative, a similar scenario unfolded for some CFC inhalers that had generic competition prior to the HFA switch; generic products were pulled from the market in favor of higher cost reformulated products.[206] In fact, the FDA also forced OTC options containing CFCs—like Primatene Mist—off the market, which created additional gaps in access to asthma therapies.[207]

5. Avoiding abrupt market discontinuation

For certain public health product hops, public health and safety may favor urgent removal or discontinuation of a product. This sort of hard switch can have devastating consequences to patients, so much so that delaying discontinuation of the originator product may still be preferable.

One example is OxyContin, which was reformulated in 2013 to a formulation that was less susceptible to misuse via intranasal and intravenous routes. Given the level of abuse of OxyContin at the time,[208] the product hop seemed justifiable on public health grounds. However, the abrupt discontinuation of non-ADF formulations led to disruptions in black market supply of OxyContin, to the extent that many individuals seeking OxyContin tablets turned to more dangerous alternatives like heroin.[209] Even with a strong public health justification, a hard switch was not warranted in this setting. Unless

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204. Aaron S. Kesselheim & Daniel H. Solomon, *Incentives for Drug Development—the Curious Case of Colchicine*, 362 NEW ENG. J. MED. 2045, 2046 (2010); Grace Farris, *The Price of Progress*, FARRIS GRACE: CUP JO COMICS (Dec. 4, 2018), https://farrisgrace.com/comics-about-medicine [https://perma.cc/P25N-KMDH] (illustrating the increasing cost of colchicine in a comical cartoon).

205. Kesselheim & Solomon, *supra* note 204, at 2046.

206. *See generally* Wouters et al., *supra* note 92, at 1153–54 (explaining the market shift from CFC inhalers to HFA devices).

207. *See id.* (asserting people had to pay monopoly prices for products that were therapeutically equivalent due to the ban on CFC products).

208. *See U.S. Opioid Dispensing Rate Maps*, *supra* note 119 (finding the number of dispensed prescriptions peaked at 255 million in 2012) ("[T]he total number of prescriptions dispensed peaked in 2012 at more than 255 million and a dispensing rate of 81.3 prescriptions per 100 persons.").

209. *See* Evans et al., *supra* note 135, at 7.

measures are put in place to proactively ensure continued access to new products, soft switches are still preferable to hard switches.

B. Should Incentives Be Needed?

Many of the existing incentives for pharmaceutical development are designed to try to encourage manufacturers to begin costly research in new areas of medicine. In contrast, public health mandates or evolving scientific information may warrant less substantial changes to an existing product. Given that the time and expenditures are likely to be less, should manufacturers need additional incentives to comply? Do we need to offer another proverbial carrot when a stick could work just as well?

1. The European approach

In Europe, product hops are commonly characterized as line extensions and are not subject to any additional exclusivities. Thus, when reformulated products receive new market exclusivity periods in the United States, they may launch those new products in Europe, but they do not receive more exclusivity.[210] Further, they may have to justify the added value of their products to health technology assessment bodies in order for these products to be utilized in those countries.[211] This was the case with Nexium (esomeprazole), which was a product hop from Prilosec (omeprazole).[212] Even though the new product sold

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210. *See* European Commission Press Release IP/23/1843, European Health Union: Commission Proposes Pharmaceuticals Reform for More Accessible, Affordable, and Innovative Medicines, (Apr. 26, 2023) (restricting extension of market exclusivity to a list of enumerated reasons).

211. *See Health Technology Assessment Bodies*, EUR. MED.'S AGENCY, https://www.ema.europa.eu/en/partners-networks/health-technology-assessment-bodies [https://perma.cc/8RWP-JRFP] (noting the parallel consultation procedure with European Medicines Agency and health technology assessment bodies).

212. *See* Jonathan J. Darrow, *The Patentability of Enantiomers: Implications for the Pharmaceutical Industry*, 2 STAN. TECH. L. REV. 2, 3 (2007) (explaining why the unique structural characteristics of chiral molecules present challenges to patentability on the bases of novelty and non-obviousness); *see also* Charles Duan, *Product Hopping: Federal and State Approaches*, R ST. (Mar. 2021), https://www.rstreet.org/wp-content/uploads/2021/03/Final-No.-227.pdf [https://perma.cc/S8HF-9JPT] ("Omeprazole is a mixture of two enantiomers; that is, two molecules that are identical in composition but mirror images of each other, as a left hand is to a right. Esomeprazole was just one of the two molecules. While one isolated enantiomer can sometimes perform better than the mixture, the evidence of benefit simply was not there for esomeprazole.").

billions in the United States, it was not as profitable in Europe because it had not earned any additional exclusivity in that market.[213]

2. Mandated studies

As noted previously, PREA permits the FDA to mandate pediatric studies of drugs—old or new—for which the FDA believes pediatric safety or effectiveness information is important to consumers and prescribers, such as in the case of increased off-label use in children.[214] Though manufacturer compliance with PREA has been inconsistent,[215] the approach could have benefits in the context of public health product hops.[216]

The FDA could mandate that a manufacturer develop and study a new formulation of a drug that may have public health benefits. For instance, when the Teleflex intranasal naloxone kit with atomizer was recalled from the market because the atomizer was not effectively delivering the medication in an "atomized plume,"[217] the FDA could have mandated that the manufacturer of brand-name intravenous naloxone develop an intranasal delivery device for its opioid overdose reversal drug. Instead, this work was done with considerable research support from federal agencies, but executive authorities—government

213. *See* MARCIA ANGELL, THE TRUTH ABOUT THE DRUG COMPANIES: HOW THEY DECEIVE US AND WHAT TO DO ABOUT IT 77 (2004) ("AstraZeneca developed an audacious plan. Prilosec is a mixture of an active and a possibly inactive form (called isomers) of the omeprazole molecule. The company would take out a new patent on the active form of the Prilosec molecule, name it Nexium (it wouldn't have done to call it 'Half-o'-Prilosec,' but that is what it was), and promote it as an improvement over Prilosec just in time to switch people over before the Prilosec patent expired. The plan worked.").

214. *See* Bourgeois & Kesselheim, *supra* note 176, at 875–76 (noting that the FDA can require sponsors to perform pediatric studies before market entry).

215. *See id.* at 880 (noting that most manufacturers seek to defer their pediatric studies of drugs since the FDA has limited authority to force them to conduct pediatric studies after a product gains market approval).

216. *See* Florence T. Bourgeois & Thomas J. Hwang, *The Pediatric Research Equity Act Moves into Adolescence*, 317 JAMA 259, 259 (2017) (finding that PREA could force pediatric labeling data to be available prior to products going on the market, which would prevent children from using new, more expensive products with little health gain).

217. Kounang, *supra* note 150.

patent use, march-in rights, or royalty-free licensing authorities—were not used to make the product more widely available.[218]

3. Mandated safety switches

The FDA could also drive beneficial public health product hops by mandating safety switches. Mylan became concerned about accidental injections due to mishandling of its EpiPen, so in 2009 it launched a new product with enhanced safety features.[219] Armed with new patents, the company obtained several additional years of market exclusivity as a result, successfully limiting the market penetration of rival products like Auvi-Q and Adrenaclick.[220]

Could these safety-related modifications have been mandated without any additional exclusivity? The FDA had discretion as to whether to list new patents in the Orange Book, thereby cementing their formal status as obstacles to market entry of generics.[221] Should modifications that result from safety oversights on the part of a manufacturer really lead to rewards? Now, the FTC is investigating

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218. *See generally* Letter from Legal and Public Health Experts to Elizabeth Warren, U.S. Sen., (Apr. 20, 2022) (on file with Sen. Warren), [hereinafter Letter to Senator Elizabeth Warren] https://www.warren.senate.gov/imo/media/doc/2022.4.20%20Letter%20to%20Warren%20on%20Drug%20Pricing%20Executive%20Authorities.pdf [https://perma.cc/TZ7X-TVEP] (detailing the government's ability to use § 1498 and the Bayh-Dole Act's powers to make drug products reasonably available when manufacturers fail to do so).

219. *See* Popken, *supra* note 57 (reporting the main change in 2009 was a locking mechanism to protect patients from the needle). Mylan justified price increases at the time by pointing to the costs of product redesign. *Id.*

220. Jacob S. Sherkow & Patricia J. Zettler, *EpiPen, Patents, and Life and Death*, 96 N.Y.U. L. REV. ONLINE 164, 171 (2021), https://www.nyulawreview.org/wp-content/uploads/2021/08/SherkowZettler-fin-1.pdf [https://perma.cc/B3DL-F4DD] ("While EpiPen's original design stems from a 1977 patent from one of Mylan's predecessors, Meridian Medical Technologies, the design has been reworked over the years in response to safety concerns, like accidental autoinjection. On these improvements, Meridian received at least five patents, all expiring on September 11, 2025.").

221. *Id.* at 170. In fact, there is a strong case to be made that device patents for EpiPen were improperly listed in the Orange Book. *See* Letter from Elizabeth Warren, U.S. Sen., to Dr. Robert M. Califf, Comm'r of Food & Drugs, U.S. Food & Drug Admin. (Aug. 28, 2023) https://www.warren.senate.gov/imo/media/doc/2023.08.28%20Letter%20to%20FDA%20re%20drug%20patents.pdf [https://perma.cc/GJG6-UVLJ] (proposing solutions to address the loopholes that allow drug companies to abuse the Orange Book).

whether device patents like those of the modified EpiPen should have been listed in the Orange Book at all.[222]

A better solution would be to mandate certain safety switches without offering additional incentives. Akin to modifying product labeling when safety-related information arises in the post-market period, modifying products might also be required when public health-related information arises. This would remove incentives to make "safety-like" product modifications: those that purport to make a product safer but are primarily intended to extend market exclusivities or hinder competition. This has happened for other drugs in recent memory, including Suboxone (buprenorphine/naloxone), for which the manufacturer switched formulations from a sublingual tablet to a sublingual film.[223] This successfully foreclosed generic entry for sublingual tablet formulations via the exaggeration of safety concerns.[224] Mandates would permit the FDA to evaluate and determine whether safety switches are warranted prior to mandating

222. Press Release, FTC, FTC Challenges More than 100 Patents as Improperly Listed in the FDA's Orange Book (Nov. 7, 2023), https://www.ftc.gov/news-events/news/press-releases/2023/11/ftc-challenges-more-100-patents-improperly-listed-fdas-orange-book [https://perma.cc/5JRS-LDMH]; *see also* Press release, FTC, FTC Files Amicus Brief Outlining Anticompetitive Harm Caused by Improper Orange Book Listings (Nov. 20, 2023), https://www.ftc.gov/news-events/news/press-releases/2023/11/ftc-files-amicus-brief-outlining-anticompetitive-harm-caused-improper-orange-book-listings [https://perma.cc/Y3VH-CZKS] (describing the FTC's amicus brief explaining the significant harm improper Orange Book listings can have on competition).

223. Eric J. Lavonas, S. Geoffrey Severtson, Erin M. Martinez, Becki Bucher-Bartelson, Marie-Claire Le Lait & Jody L. Green et al., *Abuse and Diversion of Buprenorphine Sublingual Tablets and Film*, 47 J. SUBSTANCE ABUSE & ADDICTION TREATMENT 27, 27 (2014) (noting the tablet formulations of buprenorphine/naloxone were introduced into the market in 2003 and the film in 2010).

224. *See* Popken, *supra* note 57 (highlighting the impact of EpiPen's product hop, including a comment from Senator Amy Klobuchar (D-MN) noting, "[i]t's hard to imagine that the changes Mylan made to its product features would come close to justifying nearly 500 percent price increases." (internal quotations omitted)); *see also* Rachel E. Barenie, Michael S. Sinha & Aaron S. Kesselheim, *Factors Affecting Buprenorphine Utilization and Spending in Medicaid, 2002–2018*, 24 VALUE IN HEALTH 182, 185 (2021) ("The product hop was aided . . . by delaying entry of a generic version of the tablet formulation . . . [I]n September 2012, the Suboxone manufacturer submitted a Citizen Petition to the FDA requesting that the agency reject drug applications for generic tablet buprenorphine-containing products for OUD owing to reports of increased pediatric exposure to buprenorphine and buprenorphine-naloxone SL tablets in 2006 and 2007.").

product changes, rather than relying on the manufacturer's assertion that safety improvements are warranted.

4. Compulsory licensing

In some cases, public health product hops generate new patent exclusivities. 3M produced its HFA inhaler and eventually other manufacturers had to follow suit, generating licensing revenues to 3M through what Charles Duan terms "mandatory infringement."[225] Instead of outsized rewards for first movers and penalties (in the form of licensing fees) to latecomers, new technology that addresses public health needs should be made widely available to all companies needing to reformulate their products.

Perhaps this could occur in conjunction with other incentives listed above. For example, a manufacturer that receives direct payments to develop its new technology should be compelled to license that technology to other competitors. Given that the FDA required all pMDI manufacturers to move to the HFA-134a propellant, they should have all been granted access to use that propellant at a reasonable cost. In this way, innovators that solve major public health problems can be rewarded without compromising public access to the innovation.

Even in the setting where a manufacturer independently funds research and development, compulsory licensing should still be an option. The federal government could use patents under 28 U.S.C. § 1498, independent of whether that technology was developed using federal funds.[226] If "reasonable and entire compensation" is paid, that technology can be made available for a limited period of time to allow other manufacturers to enter a market, which could preserve access and reasonable prices for consumers.

C. Tailoring Less Outsized Incentives for Public Health Product Hops

The better compromise may be to create incentives that more closely align with the value of the product switch. Removing CFCs in respiratory

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225. Duan, *supra* note 96, at 222 ("[M]andatory infringement . . . requires two ingredients: (1) a regulation; and (2) IP rights, such as patents or copyrights.").

226. 28 U.S.C. § 1498 allows the federal government to use any U.S. patent without license from the patent holder in exchange for "reasonable and entire compensation for such use and manufacture." *See* Christopher J. Morten & Charles Duan, *Who's Afraid of Section 1498? A Case for Government Patent Use in Pandemics and Other National Crises*, 23 YALE J.L. & TECH. 1, 12 (2020) ("[Section] 1498 can be used modestly as well as massively to achieve various public benefits—lowering prices, expanding supply, or shielding socially useful activity from the risk of liability or injunction.").

inhalers, for instance, advanced an important public health objective but provided an outsized reward in the form of decades of additional market exclusivity and profits.[227] When public health becomes the driving force for product hops, alternative rewards should be considered. Allowing a full new drug application ("NDA"), along with the regulatory and patent exclusivities that come with it, is outsized compared to the benefits the public receives. It is also important to avoid hard switches that can have unintended consequences, such as disrupted patient access, shortages, and generics being removed from the market. Even a soft switch can be disruptive when competitors cannot accelerate research and development quickly enough to develop competitor products.[228]

1. Direct funding of research and development

One approach may be for the federal government to directly fund any research and development associated with public health product hops. The federal government substantially contributes to research and development already.[229] Fully funding the research and development required to reformulate products would eliminate any impetus to recoup expenditures through market exclusivity and high prices.[230] Direct funding may be a more efficient way to develop novel products that can address imminent public health needs.[231] The federal government essentially did this for intranasal naloxone but left market dynamics intact, leading to limited access and underutilization during a crisis.[232]

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227. See discussion *supra* Section II.A.1 highlighting the low percentage of overall CFC burden attributable to respiratory inhalers.

228. Carrier & Shadowen, *supra* note 3, at 194 ("The 'added choice' of the reformulated product is actually the means by which consumers' real choice is eliminated."); *see also* Sinha, *supra* note 14, at 319–24 (discussing the challenges associated with developing complex generics of the Advair Diskus).

229. *See* Ekaterina G. Cleary, Jennifer M. Beierlein, Navleen S. Khanuja, Laura M. McNamee & Fred D. Ledley, *Contribution of NIH Funding to New Drug Approvals 2010–2016*, 115 PROC. NAT'L ACAD. SCI. 2329, 2332 (2018) ("We identified NIH-funded publications and projects directly related to all the 210 NMEs approved by the FDA from 2010–2016 or their molecular targets.").

230. *See* Popken, *supra* note 57 (noting that Senator Grassley requested an explanation of Mylan's decision to increase the price of EpiPens but received little information).

231. See discussion *supra* Section III.B.2 suggesting that funding research and development conducted by the manufacturer may be more efficient than providing federal grant support to outside entities to accomplish the same task.

232. See discussion *supra* Section II.C explaining that it was considerable federal support that allowed an intranasal naloxone device to be developed so quickly.

2. Tax credits for research and development expenditures

A commonly used incentive for research and development comes in the form of tax credits. In this way, the federal government ends up indirectly funding the costs of research and development. Providing up to 100% in tax credits for essential public-health-related innovations and public health product hops would generate new products at full cost to the taxpayer, but on the condition that there be no roadblocks that raise prices or otherwise limit access to the new product. Reasonable pricing clauses or other efforts at price caps might be justifiable in the setting of public health product hops, even if they are not broadly palatable in the United States for other uses.[233] Though direct funding may be preferable, this approach better accommodates situations in which the research budget may unforeseeably exceed a pre-allocated amount.

3. Lump sum payments after marketing

Another approach to incentivizing the production of a reformulated product to address public health needs would be a lump sum payment to the manufacturer in lieu of new product exclusivity. This amount could be scaled to a value that exceeds research and development costs, acknowledging that manufacturers may be postponing research and development into other products while developing the public-health-motivated reformulation. Though the financial outlay may be significant, lump sum payments could be conditioned on allowing generic competitors to enter the market and compete in a timely fashion. Robust generic competition would drive prices down, decreasing barriers to access.

D. Public Health-Promoting Incentives for Public Health Product Hops

In light of the mixed results produced by existing incentive structures in compelling societally beneficial research and development, a new incentive structure will be necessary for public health product hops. Importantly, that structure requires a gatekeeper function such that manufacturers cannot simply claim that their product hop offers public health benefits in order to qualify for the incentive. Incentives for public health product hops should be reserved for substantial

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233. *See generally* Jorge L. Contreras, *What Ever Happened to NIH's "Fair Pricing" Clause?*, BILL OF HEALTH (Aug. 4, 2020), https://blog.petrieflom.law.harvard.edu/2020/08/04/nih-fair-pricing-drugs-covid19 [https://perma.cc/TBT3-HJ9W] (describing previous attempts by the National Institutes of Health to curb the prices of pharmaceuticals through institution of a fair pricing clause).

crises, like the depletion of the ozone layer and the opioid crisis, for which urgent research and development was warranted to address public health needs.

1. Most product hops should continue to face FTC scrutiny

Michael A. Carrier and Steve Shadowen's "no-economic-sense test" for product hopping asks whether the brand manufacturer's "sole motive was to impair competition."[234] The "no-economic-sense test" would prevent anticompetitive product hops if the test is applied at the time of FDA review for the product hop, with input from the FTC as needed. The FDA could rely on the test, as well as information provided by the sponsor or the FTC, to deny marketing applications for late-filed product hops with anticompetitive motivations. The FDA would work with the FTC to determine the anticompetitive potential of the product hop at the point of approval—before the product has a chance to undermine competition and increase drug spending by hindering generic or biosimilar prescribing.

Screening product hops for anticompetitive potential at the point of FDA review would be more efficient than enforcement by FTC months to years after the harm to patients and payers has occurred. Importantly, the FDA's own NDA classification system makes this relatively easy for the agency to administer.[235] Type 1 NDAs cover New Molecular Entities, with no active ingredient previously approved by the FDA—these are originator products.[236] Of the remaining nine types of NDAs, many describe product hops that should face greater scrutiny prior to approval: Type 2 (New Active Ingredients, such as an ester, salt, or enantiomer); Type 3 (New Dosage Forms); Type 4 (New Combinations); and Type 5 (New Formulations).[237] In contrast, a Type 8 switch (Prescription to OTC) might be indicative of a public health

234. Carrier & Shadowen, *supra* note 3, at 210–11.

235. *See* U.S. FOOD & DRUG ADMIN., CTR. FOR DRUG EVALUATION & RSCH., MAPP 5018.2, MANUAL OF POLICY AND PROCEDURES: NDA CLASSIFICATION CODES 1–2 (2022) [hereinafter NDA CLASSIFICATION CODES], https://www.fda.gov/media/94381/download [https://perma.cc/RX99-267R] (asserting that the purpose of the classification codes is to compare approved drugs to their likely competitors already on the market); *see also* Karshtedt, *supra* note 18, at 1205 (noting NDA Classification Codes are a step toward providing clear labeling requirements for product hopping).

236. NDA CLASSIFICATION CODES, *supra* note 234, at 2–3.

237. *Id.* at 3–6.

product hop, as it may represent an effort by the manufacturer to reduce barriers to public access of an important medicine.[238]

2. An escape valve for public health product hops: short, scalable, and time-limited market exclusivity extensions

Shorter patent extensions, scaled on the basis of previous year sales, could be granted for follow-on products deemed "public health product hops," as a recognition that short extensions of market exclusivity and profits may be justifiable in certain limited circumstances. For instance, if a six-month extension could generate $3 billion in additional gross sales, a one-month extension might be more palatable to policymakers and payers. In cases when drugs are less profitable, the full six-month extension may be acceptable. The problem with patent extensions remains that other manufacturers cannot immediately enter the market to compete, which may be problematic in settings like the CFC switch, in which a robust generic marketplace was disrupted by the switch to HFAs.[239] That said, it may still be easier in certain cases to simply provide a lump sum payment if an acceptable threshold amount can be determined.

What if these short extensions were only available after the FDA issues a Written Request? Like with pediatric exclusivity, the manufacturer would be able to offer a public health product hop, but the FDA is the gatekeeper: the patent extension would only be made available once the FDA identified a public health need for the new product and issued the Written Request. In such a system, the FDA, in conjunction with the sponsor, determines whether the product hop warrants the "public health product hop" label—this could entail meetings or additional data from the manufacturer. Importantly, product hops that are unable to meet this higher standard would fail the "no-economic-sense" test, which would block their efforts to obtain FDA approval.

Congress could formalize the process by explicitly limiting a given manufacturer to one product hop per active ingredient that, in consultation with the FDA, is most likely to offer a meaningful public health benefit. That hop, if executed within the first two or three years that the originator product is on the market, would garner a scalable patent extension, but only on a single patent—unlike pediatric

238. *See id.* (noting that manufacturers making a product switch should submit the change for approval in a supplement).

239. See discussion *supra* Section II.A on the market difficulties occurring during the chlorofluorocarbon to hydrofluoroalkane inhaler product switch.

exclusivity, which provides six-month extensions to all patents, current and later-issued, covering the drug.[240]

And in cases where the public health benefits of product hops become understood later in the drug's life cycle—as happened with naloxone—exceptions to the time bar can be granted on a case-by-case basis.[241] In such cases, manufacturers would be required to provide an economic impact analysis detailing the likely costs of a late-occurring product hop with proposals for mitigating such harms, such as licensing agreements or early generic entry.

In most cases, the manufacturer knows well in advance what modifications it plans to make near the end of market exclusivity, like extended-release formulations, combination medications, alternative delivery mechanisms, and others. Patents for those products are often filed and obtained early. Many—if not most—product hops would not meet the definition of a "public health product hop" as defined here and would therefore not be eligible for a patent extension. Under the "no-economic-sense" test, those product hops would ideally be denied FDA approval or be scrutinized by the FTC as anticompetitive.

CONCLUSION

Product hops have historically been considered anticompetitive. They often represent attempts to extend market exclusivity and sustain profits from lucrative drugs, with limited additional benefits to patients.[242] In some circumstances, product hops may arise due to reasons ostensibly related to public health. In the first two case studies described here, prolonged market exclusivity and profits appear to be

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240. *See* 21 U.S.C. § 355a(c)(1)(B)(i)–(ii) (granting an additional six-month extension to whatever market exclusivity term allotted). Under this proposal, no manufacturers of HFA inhalers containing albuterol would have received scalable market exclusivity extensions because albuterol is off-patent. Newer drugs with primary patents still in force would be eligible.

241. *See* Letter to Senator Elizabeth Warren, *supra* note 218, at 4 (describing the scope in which the government would determine how to weigh the public's invention benefits). Notably, when intranasal naloxone was first marketed in late 2015, the opioid crisis was in full swing. Under this proposal, this product hop for naloxone (old drug, new delivery mechanism) could have gone straight to OTC in exchange for a patent extension on some aspect of the delivery device. *See* Saxena, *supra* note 151 ("The Clinton Health Matters Initiative is committed to efforts to reduce opioid overdose deaths, including by making naloxone more widely available." (internal quotes omitted)).

242. See discussion *supra* Part I on the perception that product hops are anticompetitive and for market gain rather than public benefit.

the dominant rationale for product hops: the FDA's push to change formulations were initially driven by industry objectives.[243]

The push to increase availability of intranasal naloxone represents a scenario in which modest incentives could have been offered to foster more robust competition and earlier OTC access. In fact, an oral contraceptive was recently approved for OTC status,[244] while other "public health product hops" have been proposed for OTC switches in the last year: albuterol rescue inhalers for asthma,[245] the abortifacient mifepristone,[246] and pre-exposure prophylaxis to prevent HIV.[247]

When public health needs merit product switches, Congress and regulatory agencies must balance the benefit to the public of the product hop against the harms that may be caused by extended market exclusivity and monopoly pricing. Public health concerns should be addressed when they arise, but not at an egregious cost to the public. Short, scalable extensions of market exclusivity, awarded early in the marketing of a product, are most likely to foster the development of new products, like extended-release versions, while limiting the costs to patients and payers.

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243. See discussion *supra* Section II.A–B on the switch to hydrofluoroalkane inhalers and abuse-deterrent formulations of Opioids and their impacts on patients and payers.

244. News Release, U.S. Food & Drug Admin., FDA Approves First Nonprescription Daily Oral Contraceptive (July 13, 2023), https://www.fda.gov/news-events/press-announcements/fda-approves-first-nonprescription-daily-oral-contraceptive [https://perma.cc/P3VE-2LAJ].

245. William B. Feldman, Jerry Avorn & Aaron S. Kesselheim, *Switching to Over-the-Counter Availability of Rescue Inhalers for Asthma*, 327 JAMA 1021, 1021 (2022) ("If manufacturers do not pursue OTC status for prescription-only rescue inhalers, the FDA should consider initiating a switch.").

246. See Lewis A. Grossman, *Freedom Not to See a Doctor: The Path Toward Over-The-Counter Abortion Pills*, 2023 WIS. L. REV. 1041, 1049 (2023) ("[S]witching the medication abortion regimen to OTC status would require FDA to somewhat re-envision the prescription requirement and the criteria for a switch. [I] argue[] that the agency should give as much consideration to the *benefits* of switching a drug as to the *risks* of doing so.").

247. *See* Douglas Krakower & Julia L. Marcus, *Free the PrEP—Over-the-Counter Access to HIV Preexposure Prophylaxis*, 389 NEW ENGL. J. MED. 481, 482 (2023) ("OTC status for oral contraceptives was approved with the understanding that the small potential increase in risk associated with making the medication available without a prescription will most likely be outweighed by the benefits—and we believe the same conclusion could be reached for . . . PrEP.").