FOR BETTER OR WORSE: EMPOWERING THE FDA TO COUNTER PATENT LAW'S PUSH FOR QUESTIONABLE DRUG MODIFICATIONS

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Pharmaceutical companies have recently faced antitrust liability for selling modified versions of previously marketed prescription drugs—an activity that, on the surface, appears at worst benign and perhaps even salutary. Nonetheless, litigation has revealed that firms sometimes change compositions of their drug products not because new formulations would lead to improved health outcomes, but because so-called secondary patents covering the new version of the drug effectively enable them to extend exclusive rights in drugs for which primary patent protection has expired. This strategy runs counter to the goal of the legislative framework for regulating branded and generic drug approvals, which is to provide incentives for discoveries that raise the quality of patient care and human health by means of appropriate periods of exclusivity for the manufacturers of branded drugs.

In this Article, I explain that the rules for patenting of chemical inventions, certain features of drug regulation under the federal Food Drug, and Cosmetic Act and its interactions with so-called "generic substitution" under state laws, and unique market forces in the pharmaceutical sector combine to create a loophole that makes undue exclusivity extensions possible. To close the loophole, I propose a novel regulatory scheme that would empower the Food and Drug Administration (FDA) to induce the generation of comparative data between related versions of drugs. I explain that the FDA is institutionally well-positioned to serve as an information intermediary that can help increase transparency with respect to drug changes and thus drive advances in the efficacy of modified versions of drugs. I argue that the proposed framework would accomplish these goals by enabling market participants to identify strategic drug changes and, in so doing, curtailing pharmaceutical manufacturers' attempts to achieve questionable exclusivity extensions. Ultimately, the FDA's new authority for comparative data development would lead to improvements in patient care and promote downstream clinical research based on scientific evidence gathered under the directives of the proposed scheme.

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INTRODUCTION

Polarized views engulf the pharmaceutical industry. "Big pharma," as the sector is often called, has drawn both praise for supplying the world with life-saving drugs and, simultaneously, scorn for keeping the prices of some of those drugs very high and occasionally engaging in questionable business practices.[2] As noted by one commentator, "despite the undisputed fact that for over a century the industry has made a major contribution to human wellbeing and the reduction of ill health and suffering, it is still regularly identified by the public in opinion surveys as one of the least trusted industries."[3] Although big pharma continues to make remarkable advancements in the field of drug development,[4] controversies ranging from the behavior of the "pharma bro"[5] to the alleged role of the industry in the opioid epidemic[6] continue to stoke negative opinions of drug-makers and bolster calls for governmental interventions.

One particular pharmaceutical industry practice that has attracted the attention of regulators, courts, and the public is so-called "product hopping."[7] A product-hopping strategy generally unfolds as follows. After receiving approval from the Food and Drug Administration (FDA), a brand pharmaceutical company typically markets a drug product exclusively, i.e., without any competition from other manufacturers, thanks to patents covering that product.[8] As these "pioneering" patents approach expiration, the company obtains new patents covering a modification of the product—for example, a so-called "extended-release" version of the original drug—and secures FDA approval for this version.[9] The company then begins to market the new product heavily, while

[2] For examples of recent leading works on the two sides of the debate, see DAVID HEALY, PHARMAGEDDON (2012); THOMAS P. STOSSEL, PHARMAPHOBIA (2015). Even the titles are telling.
[3] David Taylor, *The Pharmaceutical Industry and the Future of Drug Development*, 41 ISSUES ENV. SCI. & TECH. 1, 1 (2016).
[4] *See, e.g.*, Sarah Knapton, *First Migraine Drug in 20 Years Can Half Number of Attacks*, THE TELEGRAPH (Nov. 30, 2017), http://www.telegraph.co.uk/science/2017/11/30/first-migraine-drug-20-years-can-half-number-attacks-study-shows.
[5] Laura Lorenzetti, *Here's Why Turing Pharmaceuticals says 5,000% Price Bump Is Necessary*, FORTUNE (Sept. 22, 2015), http://fortune.com/2015/09/21/turing-pharmaceuticals-martin-shkreli-response.
[6] Alana Semuels, *Are Pharmaceutical Companies to Blame for the Opioid Epidemic?*, THE ATLANTIC (June 2, 2017), https://www.theatlantic.com/business/archive/2017/06/lawsuit-pharmaceutical-companies-opioids/529020/
[7] *See* HERBERT HOVENKAMP ET AL., IP AND ANTITRUST: AN ANALYSIS OF ANTITRUST PRINCIPLES APPLIED TO INTELLECTUAL PROPERTY LAW §§ 12.5, 15.3c (2d ed. 2009).
[8] Although pioneering products can also be supported by non-patent exclusivities, product-hopping is most often tied to patent expiration. *See infra* notes _-_ and accompanying text.
[9] For a leading example from case law, see New York *ex rel.* Schneiderman v. Actavis plc, 787 F.3d 638 (2d Cir. 2015).

deemphasizing the version that is about to go off-patent. In the more aggressive cases, the brand company might malign the original version or even take it completely off the market, thereby forcing a switch to the new version.[10] After the patent covering the pioneering product expires, other companies—after undergoing their own, shortened FDA approval processes—can offer "copies" of the original product as relatively cheap, so-called "generic" alternatives of the original version as contemplated by the federal Food, Drug, and Cosmetic Act (FDCA).[11] But a product-hopping strategy can render that version obsolete and shift the market to the newly patented, more expensive modification.

A company's decision to stop marketing one product and replace it with another does not generally strike one as problematic.[12] This sort of thing, it seems, happens in the marketplace all the time. But in the pharmaceutical context, product hopping has generated controversy partly because drugs are not normal products. Prior to marketing a drug, the brand company must, as part of the approval process, demonstrate to the FDA that the product is safe and effective for treating a particular condition based on "substantial evidence"[13]—an expensive process requiring drug discovery, chemical synthesis, preclinical studies, and extensive clinical trials.[14] And once the FDA greenlights the drug, consumers do not simply pick it up off the shelf. Typically, a patient can obtain access to a newly approved drug only when a doctor prescribes it after he or she decides that the drug is appropriate for the patient's condition.[15] The patient, moreover, rarely pays the full cost of the drug out of pocket—instead, the expense is generally largely covered by the patient's insurer.[16] This admittedly oversimplified sketch of how drugs enter and move through the marketplace shows that they are unlike other

[10] *See, e.g.*, *id.* at 647-49; *In re* Suboxone (Buprenorphine Hydrochloride and Naloxone) Antitrust Litig., MDL No. 2445, 2017 WL 3967911, at *9 (E.D. Pa. Sept. 8, 2017), *further proceedings*, 2017 WL 4910673, at *11 (E.D. Pa. Oct. 30, 2017); Abbott Labs. v. Teva Pharm. USA, Inc., 432 F. Supp. 2d 408, 420, 423-24 (D. Del. 2006).
[11] *See* 21 U.S.C. § 355(j); *see generally* 52 Stat. 1040 (1938), *codified at* 21 U.S.C. § 301 *et seq*.
[12] *But cf.* Bernard Chao, *Horizontal Innovation and Interface Patents*, 2016 WIS. L. REV. 288 (arguing that there may be anticompetitive product changes in industries other than pharma); *see also* Kenneth A. Bamberger & Orly Lobel, *Platform Market Power*, 32 BERKELEY TECH. L.J. _ (2017).
[13] *See* 21 U.S.C. § 355(b); *id.* § 355(d); *id.* § 393(b)(2)(B).
[14] *See generally* U.S. FOOD AND DRUG ADMIN., *New Drug Application (NDA)*, https://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/NewDrugApplicationNDA/default.htm (providing an overview of the approval process for new drugs); *see also* Henry G. Grabowski & John M. Vernon, *Effective Patent Life in Pharmaceuticals*, 19 INT. J. TECH. MGMT. 98 (2000).
[15] *See* 21 U.S.C. § 353(b)(1)(A).
[16] *See* Michael A. Carrier, *Real-World Analysis of Pharmaceutical Settlements: The Missing Dimension of Product Hopping*, 62 FLA. L. REV. 1009, 1011, 1017-18 (2010).

consumer products, such as cars, computers, or toasters. As explained in one court decision, in this context "the ordinary market forces that would allow consumers to consider price when selecting a product are derailed."[17]

To further underscore the unusual nature of the drug market, consider an additional layer of regulation coming from the states. For branded drugs for which generic counterparts are available, all fifty states allow (and some mandate) pharmacists to fill a prescription with a generic even when the doctor prescribes the brand.[18] An analogy outside the drug context illustrates just how odd this scheme is: suppose a customer wishes to buy a Softsoap-brand liquid hand soap at CVS and brings a bottle of it to the counter, only to have the cashier substitute Softsoap with the CVS house brand, Total Home. Unthinkable in the context of regular products, such "generic substitution" is standard fare for drugs as a means of keeping prices low.[19] The substitution, however, is allowed only when the FDA has determined that the two versions are "therapeutic equivalents,"[20] as brands and their corresponding generics must normally be. Brands, naturally, would typically like to avoid the effect of the substitution laws, and a switch to a modified, patent-protected product that is not a therapeutic equivalent of the original enables them to do so within the current regulatory framework.

A switch to a new form of a drug can be a form of salutary incremental innovation, which—while sometimes drawing condemnation as "gaming the system" by avoiding generic substitution[21]—is sometimes crucial for improved health outcomes.[22] Let

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[17] *In re* Suboxone (Buprenorphine Hydrochloride and Naloxone) Antitrust Litig., 64 F. Supp. 3d 665, 683-84 (E.D. Pa. 2014).

[18] *See* Aaron S. Kesselheim & Jonathan J. Darrow, *Hatch-Waxman Turns 30: Do We Need a Re-designed Approach for the Modern Era*, 15 YALE J. HEALTH POL'Y, L. & ETHICS 293, 311-12 (2015) (tracing the evolution of generic substitution laws).

[19] Although many states passed generic substitution laws before the FDCA was amended to usher in the current federal brand-generic regime, the role of state law as a complement to modern federal drug regulation has been recognized after the amendments. Alison Masson & Robert L. Steiner, FED. TRADE COMM'N., *Generic Substitution and Prescription Drug Prices: Economic Effects of State Drug Product Selection Laws: Staff Report of the Bureau of Economics* (1985).

[20] *See* U.S. FOOD AND DRUG ADMIN., *Orange Book Preface*, https://www.fda.gov/Drugs/DevelopmentApprovalProcess/ucm079068.htm.

[21] *See, e.g.*, Robin Feldman & Connie Wang, *May Your Drug Price Be Ever Green*, https://ssrn.com/abstracts=3061567.

[22] *See, e.g.*, Christopher M. Holman, *In Defense of Secondary Pharmaceutical Patents: A Response to the UN's Guidelines for Pharmaceutical Patent Examination*, 50 IND. L. REV. 759 (2017); Joshua Cohen & Kenneth Kaitin, *Follow-on Drugs and Indications: The Importance of Incremental Innovation to Medical Practice*, 15 AM. J. THERAPEUTICS 89 (2008); Albert I. Wertheimer & Thomas M. Santella, *Pharmaceutical Evolution: The Advantages of Incremental Innovation in Drug Development*, COMPETITIVE ENTERPRISE INSTITUTE (Apr. 2009),

us return to the extended-release example mentioned above as perhaps the paradigmatic illustration of such a drug change. Again simplifying, extended-release versions of drugs differ from their immediate-release counterparts in that—as the terms suggest—the former are engineered so as to discharge the active pharmaceutical ingredient (i.e., the working part of the drug) into the bloodstream more slowly or at least in a more controlled manner than the latter.[23] Because gradual discharge of the active ingredient usually helps ensure that less of the drug passes through the body without acting on the intended biological target, extended-release formulations can provide the same therapeutic benefit from less frequent dosing, which can in turn help increase patient compliance.[24] Moreover, such formulations could have other comparative health benefits over "regular" versions—for example, reduced side effects due to the fact that the body is not "flooded" with the drug.[25]

But for certain drugs, extended-release versions could also exhibit *reduced* efficacy compared to their immediate-release counterparts.[26] As Dr. David Kessler, then the Commissioner of Food and Drugs, explained in a speech to the Controlled Released Society in 1993, some extended-release drugs can be more susceptible than immediate-release ones to the so-called "food effect," which occurs when meals taken during the period of a drug's discharge interfere with its absorption and, potentially, action on the relevant biological targets.[27] After discussing other ways in which extended release formulations could actually reduce drug performance, Dr. Kessler did make clear that these drug modifications sometimes do lead to "real clinical and real commercial advantage."[28] More importantly, he exhorted his audience to "[t]hink in terms of clinical outcomes. Demonstrated, documented, and rigorously established improvements to patient care."[29]

Dr. Kessler's call has unfortunately not been heeded, leading to problematic forms of product hopping that this Article addresses. In spite

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http://cei.org/sites/default/files/Wertheimer%20and%20Santella%20-%20Pharmaceutical%20Evolution.pdf.

[23] *See, e.g.*, Ali Nokhodchi et al., *The Role of Oral Controlled Release Matrix Tablets in Drug Delivery Systems*, 2 BIOIMPACTS 175 (2012).

[24] *Id.* at 176.

[25] *Id.* at 175; Marilou Powers Cramer & Samuel R. Saks, *Translating Safety, Efficacy and Compliance into Economic Value for Controlled Release Dosage Forms*, 5 PHARMACOECONOMICS 482 (1994).

[26] *See generally Remarks by David A. Kessler M.D., Commissioner of Food and Drugs at a Controlled Release Society Meeting, July 27, 1993*, 4 FOOD & DRUG REP. 437 (1993) (summarizing potential problems).

[27] *Id.* at 438, 440.

[28] *Id.* at 438.

[29] *Id.*

of the sometimes unpredictable clinical effects of changes in the inactive ingredients of small-molecule drugs, the FDA generally does not evaluate comparative advantages or disadvantages of reformulated versions, and brand companies, sometimes referred to as "sponsors," do not have to obtain such data and provide it to the FDA.[30] Indeed, other than the standard requirement of proof of safety and effectiveness over a placebo,[31] the agency does not require the sponsor to give it any information on how the new version of the drug compares to the previous one, and such data is, oddly enough, often completely unavailable at the time the new version enters the market. Although the FDA does have some mechanisms that could encourage and reward the submission of data that may be relevant to comparative drug effectiveness,[32] the lengthy term of patent protection can dwarf any exclusivity period that the FDA is currently empowered to provide,[33] rendering that form of protection unnecessary for brand companies that have obtained patents covering reformulated products. As a result, product changes can sometimes be driven not by increased clinical benefits, but principally by the availability of patent protection for a new version of a drug.[34] In these circumstances, moreover, clinicians are often left without adequate data to allow them to make informed treatment decisions,[35] and payers are likewise uncertain whether to cover the cheaper off-patent version of the drug, the more expensive patented version, or both.

If the requirements of patentability gave a significant role to comparative clinical effectiveness, this critique could be moot. But they do not. Patent applications are filed early in the research process,[36] before much clinical data is available,[37] and—in any event—substantive provisions of the Patent Act account for patient benefits of drugs only tangentially. For example, the Patent Act's requirement that a patent

[30] There are some exceptions. *See, e.g.*, U.S. FOOD AND DRUG ADMIN., *Non-Inferiority Clinical Trials to Establish Effectiveness: Guidance for Industry* (Nov. 2016), https://www.fda.gov/downloads/Drugs/Guidances/UCM202140.pdf.
[31] *See* 21 U.S.C. § 355(b)(1).
[32] *See, e.g.*, *id.* § 355(c)(3)(E)(iii)-(iv) (providing for a three-year marketing exclusivity for drug modifications for which the sponsor conducted new clinical investigations essential to approval).
[33] This discussion assumes that so-called "secondary" patents have terms extending significantly beyond the expiration of the terms of "primary" patents, a scenario that often holds in practice. *See infra* notes _-_ and accompanying text.
[34] New York *ex rel.* Schneiderman v. Actavis plc, 787 F.3d 638, 658-60 (2d Cir. 2015) (providing an example of such a pretextual change).
[35] *See infra* notes _-_ and accompanying text.
[36] *See generally* Ted Sichelman, *Commercializing Patents*, 62 STAN. L. REV. 341 (2020); *see also* Shashank Upadhye, *To Use or Not to Use: Reforming Patent Infringement, the Public Use Bar, and the Experimental Use Doctrine As Applied to Clinical Testing of Pharmaceutical and Medical Device Inventions*, 4 MINN. INTELL. PROP. REV. 1, 4 (2002)
[37] *See* Jonathan J. Darrow, *Pharmaceutical Gatekeepers*, 47 IND. L. REV. 403 (2014).

claim be non-obvious[38] primarily focuses on whether the claim embodies a sufficiently inventive cognitive leap over what is already known,[39] and relegates commercial success and other factors that might stand in for improvements in patient care to "secondary considerations,"[40] which sometimes receive scant attention from courts.[41] Likewise, the patent law's utility requirement does not demand that the applicant show that the new invention is in any way better or more useful than what was previously known.[42] This doctrine is very well-entrenched in patent law.[43]

Even when drug-related data is available and might bear on patentability, examiners at the U.S. Patent and Trademark Office (PTO) can be ill-prepared to consider it and—as the central example in this Article will show—sometimes accept patent applicant arguments that are frankly nonsensical from the scientific perspective.[44] Indeed, while many applications directed to extended-release formulations and the like make it past the PTO, a good number of resulting patents are considered weak.[45] Although litigation between brand and generic companies may result in invalidation of such follow-on patents, the process takes up a significant amount of time,[46] affording the brand company unjustified exclusivity while the patent is still in force.[47] In addition, competition for follow-on innovation that might lead to the development, patenting, and marketing

[38] 35 U.S.C. § 103.
[39] Gregory N. Mandel, *A Nonobvious Comparison: Nonobviousness Decisions at the PTAB and in the Federal Courts*, 24 TEX. INTELL. PROP. L.J. 403, 418 (2017).
[40] Graham v. John Deere Co. of Kan. City, 383 U.S. 1, 17-18 (1966).
[41] *See, e.g.*, Intercontinental Great Brands LLC v. Kellogg N. Am. Co., 869 F.3d 1336, 1353 (Fed. Cir. 2017) (Reyna, J., dissenting); *cf.* Arctic Cat Inc. v. Bombardier Recreational Prods. Inc., 876 F.3d 1350 (Fed. Cir. 2017).
[42] 35 U.S.C. § 103; *see* Lowell v. Lewis, 15 F. Cas. 1018, 1019 (C.C. D. Mass. 1817) (Story, J.).
[43] *See* ROBERT PATRICK MERGES & JOHN FITZGERALD DUFFY, PATENT LAW AND POLICY: CASES AND MATERIALS 201 (7th ed. 2017).
[44] *See infra* notes _-_ and accompanying text; *cf.* Abbott Labs. v. Sandoz, Inc., 544 F.3d 1341, 1355-57 (Fed. Cir. 2008) (upholding validity and enforceability of a patent containing scientifically inaccurate clinical trial information); Jacob S. Sherkow, *Patent Law's Reproducibility Paradox*, 66 DUKE L.J. 845 (2017) (discussing the general problem of inaccurate data in patent specifications).
[45] *See* C. Scott Hemphill & Bhaven Sampat, *Evergreening, Patent Challenges and Effective Market Life in Pharmaceuticals*, 31 J. HEALTH ECON. 327 (2012); *see also* Shine Tu, *Invalidated Patents and Associated Patent Examiners*, 18 VAND. J. ENT. & TECH. L. 135, 153 (2015) (finding that the biotechnology and organic chemistry technology center art unit is responsible for the highest percentage of invalidated patents of all the art units).
[46] *See id.*
[47] *See, e.g.*, Bayer Healthcare Pharm., Inc. v. Watson Pharm., Inc., 713 F.3d 1369 (Fed. Cir. 2013) (holding invalid a patent originally granted in 1998 and reissued in 2002, and which began to be litigated in 2007). The Federal Circuit, to be sure, granted an emergency stay of district court's injunction against the defendants' ANDA approvals a month prior issuing the decision reversing the judgment that the patents are not invalid. *See* Order, Bayer Healthcare Pharm., Inc. v. Watson Pharm., Inc., No. 13-1207 (Fed. Cir. Mar. 13, 2013), ECF No. 57.

of alternative drug improvements by third parties is limited for various reasons. First, brand companies that have developed the original drug have a head start over others in terms of valuable internal know-how related to the drug to be improved,[48] and, second, they can get ahead of competition on modifications thanks to both patents and to non-patent exclusivities that one commentator has termed "regulatory competitive shelters."[49] Because of the constrained competition, the field is characterized by information asymmetries both with respect to health impacts of follow-on formulations and the patents that cover them.

In this Article, I argue that new approaches involving FDA-administered regulation of certain types of cumulative pharmaceutical innovations are necessary to supplement the existing patent-based mechanisms in order to provide incentives for companies that generate useful comparative data.[50] Such data would, in turn, help increase the transparency of pharmaceutical product markets. In the context of drug reformulations, a patent is not a signal of clinical impact of a follow-on drug relative to the original version, and sometimes not even a guarantee that the "improvement" represents a robust technical advance over the pioneering drug. Accordingly, the dominant role of patents as the instrument for inducing this subset of pharmaceutical innovation is difficult to justify.[51] Instead, I explore FDA-driven mechanisms that meaningfully reward manufactures who provide comparative data on drug reformulations as opposed to those who do not. This information is more relevant than patent coverage to the function of drugs, which is to improve health outcomes.

I also contend that greater clarity about comparative drug information coming from the FDA can relieve pressure from other decision-makers, including courts deciding antitrust cases. A growing number of courts have concluded that allegations of product hops, particularly when accompanied by a "hard switch" (i.e., complete removal of the previous version of the drug from the market), state a

[48] *See* Anna B. Laakmann, *A Property Theory of Medical Innovation*, 56 JURIMETRICS J. (2016); W. Nicholson Price II, *Expired Patents, Trade Secrets, and Stymied Competition*, 92 NOTRE DAME L. REV. 1611 (2017); *see also* W. Nicholson Price, *Regulating Secrecy*, 91 WASH. L. REV. 1769 (2016).

[49] Yaniv Heled, *Regulatory Competitive Shelters*, 76 OHIO ST. L.J. 299 (2015); *see also* Robin Feldman, *Regulatory Property: The New IP*, 40 COLUM. J. L. & ARTS 53 (2016).

[50] *Cf.* Yaniv Heled, *Patents vs. Statutory Exclusivities in Biological Pharmaceuticals—Do We Really Need Both?*, 18 MICH. TELECOMM. & TECH. L. REV. 419 (2012) (proposing deemphasizing patents in the regulation of large-molecule drugs); *see also* Douglas L. Rogers, *Double Patenting: Follow-on Pharmaceutical Patents that Suppress Competition*, 14 NW. J. TECH. & INTELL. PROP. 317 (2017).

[51] *Cf.* Lara J. Glasgow, *Stretching the Limits of Intellectual Property Rights: Has the Pharmaceutical Industry Gone Too Far?*, 41 IDEA 227, 228 (2001).

monopolization claim under § 2 of the Sherman Act.[52] In one case, *New York ex rel. Schneiderman v. Actavis plc*, the Court of Appeals for the Second Circuit affirmed a finding of an antitrust violation based in part on record evidence that the brand company advanced only pretextual reasons to stop selling the pioneering version of the drug, and engaged in a product hop so as to avoid competition.[53] Brand company actions giving rise to cases like *Actavis* have drawn the attention of Dr. Scott Gottlieb, the current Commissioner of Food and Drugs, who recently stated that the FDA is considering "a group of policies aimed at closing loopholes that allow branded drug companies to game our rules in ways that forestall the generic competition that Congress intended"[54] after specifically calling out "[p]ost-approval changes to innovator drug products, e.g., reformulations"[55] in a request for public comments.

Although we are yet to see what measures the Commissioner might take—referring potentially problematic cases to the Federal Trade Commission (FTC) for antitrust scrutiny is one possibility[56]—antitrust law is an uneasy fit in this area. Historically, antitrust has been conceived of as a form of government regulation, via legal enforcement actions, of conduct that lowered consumer welfare when companies were left to their own devices.[57] Therefore, skepticism about relying on antitrust to further micromanage an already highly regulated industry is understandable.[58] In addition, although antitrust actions have to date been the only remedy available to deal with certain product-hopping practices, commentators have expressed concern that these cases have stretched antitrust law to its limits, noting that "policymakers should not distort well-established

[52] For the latest example so far, see *In re* Suboxone (Buprenorphine Hydrochloride and Naloxone) Antitrust Litig., MDL No. 2445, 2017 WL 4910673, at *11 (E.D. Pa. Oct. 30, 2017).
[53] 787 F.3d 638, 658-60 (2d Cir. 2015).
[54] Scott Gottlieb, M.D., U.S. FOOD AND DRUG ADMIN.: FDA VOICE BLOG, *Reducing the Hurdles for Complex Generic Drug Development* (Oct. 2, 2017), https://blogs.fda.gov/fdavoice/index.php/2017/10/reducing-the-hurdles-for-complex-generic-drug-development.
[55] U.S. FOOD AND DRUG ADMIN., *Administering the Hatch-Waxman Amendments: Ensuring a Balance Between Innovation and Access; Public Meeting; Request for Comments* at 8 (June 14, 2017), https://s3.amazonaws.com/public-inspection.federalregister.gov/2017-12641.pdf.
[56] I joined a group of public commenters who suggested this approach to the FDA. Comments of Ameet Sarpatwari, Aaron S. Kesselheim, Michael A. Carrier, and Dmitry Karshtedt, *Administering the Hatch-Waxman Amendments: Ensuring a Balance Between Innovation and Access*, Docket FDA-2017-N-3615 (Sept. 18, 2017), https://www.regulations.gov/document?D=FDA-2017-N-3615-0064.
[57] *See, e.g.*, United States v. South-Eastern Underwriters Ass'n, 322 U.S. 533, 552-53 (1944) (describing antitrust law as a form of "regulation" under the Commerce Clause).
[58] *Cf.* Douglas H. Ginsburg al., *Product Hopping and the Limits of Antitrust: The Danger of Micromanaging Innovation*, COMPETITION POL'Y INT'L ANTITRUST CHRON., Dec. 2015, at 1.

antitrust rules in order to solve what is, at heart, a regulatory problem."[59] Finally, there are legitimate questions with respect to whether courts have the institutional capacity to engage in the balancing of competitive harms and benefits of drug product changes that must sometimes take place in antitrust cases[60]—and even if the courts had that capacity, whether addressing such problems ex post, after the alleged harms may have already eventuated, is adequate from the social welfare perspective.

In contrast to the PTO and to courts deciding antitrust cases, the FDA is ideally positioned to at least weigh in on the question of whether a pharmaceutical product change is pretextual or "sham"[61]—embodying a practice that has also been labeled with a pejorative term "evergreening"[62]—as opposed to a potentially socially valuable drug modification. The agency already examines vast quantities of drug-related clinical data and, in some circumstances, it must develop a view on how two or more different treatments compare and can ask for data that could aid various stakeholders in making that determination.[63] This Article proposes further leveraging the FDA's expertise in evaluating drug products into incentive mechanisms for generating information that will help physicians and payers evaluate how a follow-on drug product stacks up against the earlier version.

In its mildest form, the FDA's new charge could simply take the form of inviting drug sponsors to submit comparative drug data to the FDA—showing, for example, that the efficacy of a reformulated (e.g., extended-release) drug is just as unaffected by food intake as that of the previous version, or that the drug works particularly well compared to the

[59] Alan Devlin & Michael Jacobs, *Anticompetitive Innovation and the Quality of Invention*, 27 BERKELEY TECH. L.J. 1, 51 (2012).

[60] Abbott Labs. v. Teva Pharm. USA, Inc., 432 F. Supp. 2d 408, 420, 423-24 (D. Del. 2006); *see* Hillary Greene, *Muzzling Antitrust: Information Products, Innovation and Free Speech*, 95 B.U. L. REV. 35, 75-79 (2015). Of course, the first lines of inquiry in these antitrust cases are whether the defendant has monopoly power and has engaged in exclusionary conduct. *See id.* at 79-80.

[61] *Cf.* Dennis W. Carlton et al., *Does FTC's Theory of Product-Hopping Promote Innovation?*, 21. J. COMPETITION L. & ECON. 495, 503-06 (2016) (seeing a great role for the FDA in combatting anticompetitive conduct); *see also* Aidan Hollis, *Me-too Drugs: Is There a Problem*, http://www.who.int/intellectualproperty/topics/ip/Me-tooDrugs_Hollis1.pdf (similar); Rebecca S. Eisenberg & Daniel A. Crane, *Patent Punting: How FDA and Antitrust Courts Undermine the Hatch-Waxman Act to Avoid Dealing with Patents*, 21 MICH. TELECOMM. & TECH. L. REV. 197 (2015) (arguing for greater involvement of the FDA evaluating patent-related issues); Joseph Fielding, Note, *From Pay-for-Delay to Product Hopping: The Limited Utility of Antitrust Law in the Pharmaceutical Industry*, 38 CARDOZO L. REV. 915 (2017) (similar).

[62] Feldman & Wang, *supra* note 21; *see also* Amy Kapczynski et al., *Polymorphs and Prodrugs and Salts (Oh My!): An Empirical Analysis of "Secondary" Pharmaceutical Patents*, 7 PLoS ONE e49470 (2012); Aaron S. Kesselheim et al., *Extensions of Intellectual Property Rights and Delayed Adoption of Generic Drugs: Effects on Medicaid Spending*, 25 HEALTH AFFAIRS 1637 (2006).

[63] *See infra* notes _-_ and accompanying text.

earlier version in terms of inducing compliance in some patient sub-population (e.g., teenagers).[64] If the data is submitted, the FDA could review the relevant study, summarize it, and have the information revealed by the study added to the drug package insert, or "label," for doctors, patients, and payers to peruse.[65] In contrast, if no comparative study was performed, the agency could require a label notation to that effect as well, putting the relevant audiences on clear notice of this fact. As I discuss in the Article, more significant interventions to differentiate between companies that attempt to develop clinically valuable drug improvements and those that do not are also conceivable.

Under this framework, the FDA's involvement could help increase transparency in an area characterized by information asymmetries stemming from the "credence-good" nature of drugs,[66] and help correct for the lack of robust market-based checks on pharma company claims given the rarity of competition for drug improvements.[67] In serving as a clearinghouse for comparative data on related drug versions, the FDA could send useful market signals physicians and payers and, in the process, help even out these disparities. In addition, the FDA's involvement could pave the way for more vigorous marketing by brand companies when comparative data is in fact provided,[68] as well as for enabling immunity from antitrust enforcement actions based on product hops.[69]

A regulatory scheme that differentiates companies that attempt to reformulate drugs with the aim of providing increased clinical benefits from those that do it pretextually in an effort to maintain exclusivity can bring with it many social benefits. Indeed, even champions of follow-on pharmaceutical research note that "it is imperative to separate the constructive process of incremental innovation from transparent attempts to extend patent protection periods with minor modifications of little therapeutic advantage."[70] This Article explores ways in which the FDA could do so, thereby reducing the unduly dominant role of patents in this

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[64] *See infra* notes _-_ and accompanying text.
[65] *See* U.S. FOOD AND DRUG ADMIN., *Labeling Information for Drug Products*, https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/default.htm (providing general information on drug labels).
[66] Ariel Katz, *Pharmaceutical Lemons: Innovation and Regulation in the Drug Industry*, 14 MICH. TELECOMM. & TECH. L. REV. 1, 11-13 (2007).
[67] *See infra* notes _-_ and accompanying text.
[68] *Cf.* Coleen Klasmeier, *Congress Should Clarify the Circumstances Under Which Drug Makers Can Communicate Results on Comparative Effectiveness*, 31 HEALTH AFFAIRS 2220 (2012).
[69] Immunity would be based on the fact that the drug changes are not pretextual, a fact that would almost certainly eliminate antitrust liability.
[70] Wertheimer & Santella, supra note 22, at 7.

area. The data generated in the process can contribute to the program of comparative effectiveness research (CER), which has been a significant national priority at least since the National Recovery and Reinvestment Act of 2009[71]—and which requires production of "data prior to the widespread adoption of a drug or treatment" in order to be successful.[72]

A regulatory information-inducing regime for rewarding those who supply the relevant data over those who do not is particularly justifiable as a mechanism for advancing this goal because "[r]esearch into the comparative efficacy of tests and treatments is a classic public good,"[73] whose under-production, as economic theory suggests, could be remedied with appropriate incentive structures. In addition, the information generated thereby would be useful not only to clinicians, but to future researchers as well.[74] More generally, inquiries into CER have become a significant part of modern medical care,[75] and drug companies are in an excellent position to generate initial data that could help guide clinicians' drug adoption choices and perhaps stimulate further research and development.[76] The goal of this Article, then, is to harness the FDA's established function as an information-generating agency[77] to help improve transparency with respect to comparative efficacy, safety, and ultimately cost-effectiveness of related versions of drugs. Even a clear message of the fact that the relevant data is unavailable can serve as an important data point for health-care providers, patients, and payers.

The rest of this Article proceeds in five parts. Part I describes the federal statutory regime for the approval of branded and generic drugs, and also covers state generic substitution laws and their role in realizing cost savings associated with generic entry. Part II explains the role of patents in incentivizing the development of both pioneering and follow-on drugs, provides the relevant background on patent law, and details product-hopping practices. Part III discusses information asymmetries

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[71] 42 U.S.C. § 299b.

[72] G. Caleb Alexander & Randall S. Stafford, *Does Comparative Effectiveness Have a Comparative Edge?*, 301 J. AM. MED. ASS'N 2488, 2488 (2009); *see also* Alec B. O'Connor, *Building Comparative Efficacy and Tolerability into the FDA Approval Process*, 303 J. AM. MED. ASS'N 979 (2010).

[73] M. Gregg Bloche, *The Emergent Logic of Health Law*, 82 S. CAL. L. REV. 389, 445 (2009).

[74] *See generally* Rebecca S. Eisenberg, *The Role of the FDA in Innovation Policy*, 13 MICH. TELECOMM. & TECH. L. REV. 345 (2007).

[75] For an overview, see CAROL M. ASHTON & NELDA P. WRAY, COMPARATIVE EFFECTIVENESS RESEARCH (2013).

[76] *See* Marc L. Berger & David Grainger, *Comparative Effectiveness Research: The View From a Pharmaceutical Company*, 28 PHARMACOECON. 915, 916 (2010) (calling CER "the next logical step in the progression of pharmaceutical R&D").

[77] Katz, *supra* note 66, at 27-28; *see also* George J. Stigler, *The Theory of Economic Regulation*, 2 BELL J. ECON. & MGMT. SCI. 3, 3 (1971) (explaining that regulation often benefits the regulated industry).

and other forces that interfere with efficient functioning of pharmaceutical markets, focusing on the lack of transparency with respect to data pertaining to levels of relative drug efficacy under the current, patent-dominated schemes. This Part also describes the important function of comparative effectiveness analysis in modern medical care and research, and explains ways in which drug-makers and the FDA could play a bigger role in the generation of data useful for this program. Part IV advances a series of approaches for enlisting the FDA's expertise to reward pharmaceutical companies that generate comparative data between closely related versions of drugs that they market, and discusses advantages and disadvantages of each. Before the Article concludes, Part V considers and answers some objections to the expanded role of the FDA in the inducement of comparative drug data generation.

I. THE FEDERAL HATCH-WAXMAN REGIME AND STATE-LAW GENERIC SUBSTITUTION

The Drug Price Competition and Term Restoration Act, an amendment to the FDCA often referred to simply as the Hatch-Waxman Act,[78] is a statutory scheme for regulating small-molecule drugs in which both the FDA and the PTO play distinct but interrelated roles. The purpose of the Act is to balance incentives for discovery and development of drugs against the goal of making medicines available to consumers at reasonable prices.[79] The Act contemplates two types of players: brand and generic manufacturers.[80] At bottom, the Hatch-Waxman Act, in conjunction with the Patent Act, provides for exclusive rights for brand companies to market new drugs that they develop, while also facilitating the market entry of generic equivalents of branded drugs once the exclusivities expire.[81]

This general scheme reflects the relative burdens faced by brand and generic manufacturers. The brands do the work of identifying promising drug targets, synthesizing candidate chemical compounds in useful quantities and fully characterizing them, conducting in vitro and in vivo studies as well as several phases of human clinical trials to prove the drug's safety and effectiveness, engaging in the back-and-forth with the FDA in order to secure approval, and establishing a market for the drug through extensive promotion and sampling to doctors and patients.[82] The

[78] Pub. Law 98-417, 98 Stat. 1585 (Sep. 24, 1984).
[79] *See* H.R. Rep. No. 98-857, pt. 1, at 14-15 (1984), *reprinted in* 1984 U.S.C.C.A.N. 2647.
[80] *Id.* at 19-20.
[81] *Id.* at 15-17
[82] *See generally* DANIEL CARPENTER, REPUTATION AND POWER 465-543 (2010).

task of the generics is simpler: they must make (or contract to have made) drug products that are chemically identical to those made by the brands and approved by the FDA, while adhering to good manufacturing practices and passing certain tests confirming that what they made is "bioequivalent" to the brand.[83] Crucially, generics need not conduct extensive clinical trials, and can simply rely on data developed by the brands as evidence that the product they are making is safe and effective. The difference between brands and generics is reflected in the respective monikers of the filings that these players typically make with the FDA: brands file New Drug Applications (NDAs) while generics file *Abbreviated* New Drug Applications (ANDAs).[84] As even these terms suggest, the showings that generics must make are significantly less onerous than those of the brands.

In order to limit generic "free-riding" and thus provide incentives for brand companies to innovate, the brands are entitled to certain exclusivities. Under Hatch-Waxman, brands receive five years of FDA-enforced exclusivity for any new chemical entity approved to be marketed as a drug.[85] During this period, which runs five years from the NDA approval, the FDA is barred from considering ANDAs on drugs containing the new chemical entity, and generics manufacturers are thereby prevented from relying on the brands' clinical trial data during this time to obtain approval for their own "copies" of the drug.[86]

Even longer exclusivity can be achieved with patent rights, and that aspect of the drug-regulation regime constitutes the crux of this Article. In a PTO proceeding that is independent from the FDA drug approval process,[87] brand owners may obtain patents covering, for

[83] *See* U.S. FOOD AND DRUG ADMIN., *FDA Ensures Equivalence of Generic Drugs*, https://www.fda.gov/drugs/emergencypreparedness/bioterrorismanddrugpreparedness/ucm134444.htm. Equivalence, to be sure, need not be exact—there is some tolerability in the composition that still allows bioequivalence. *See* 21 C.F.R. 210.3(b)(2),(10); *see also* Janet Freilich, *The Paradox of Legal Equivalents and Scientific Equivalence: Reconciling Patent Law's Doctrine of Equivalents with the FDA's Bioequivalence Requirement*, 66 SMU L. REV. 59, 78-87 (2013) (describing cases in which differences between brand generic products, such as variations in inactive ingredients, did not bar a finding of bioequivalence).

[84] *Compare* 21 U.S.C. § 355(a)-(b), *with id.* § 355(j).

[85] *Id.* § 355(j)(5)(F)(ii).

[86] When the underlying patents are challenged by ANDA applicants, that period is shortened to four years. *See id.*

[87] There is a statutory provision that authorizes the PTO to request information with respect to drugs form the FDA, *see* 35 U.S.C. § 372(d), but it has not been used very often, *see* Darrow, *supra* note 37, at 402-03. For a proposal to increase interagency cooperation, though not including the PTO, see Rachel E. Sachs, *Administering Health Innovation*, 39 CARDOZO L. REV. (forthcoming 2018), https://ssrn.com/abstract=3013895. But even if there is interagency cooperation between the PTO and the FDA, the fact remains that 35 U.S.C. § 103 is not entirely suited for basing patentability on clinical benefits.

example, chemical compositions embodying the newly invented drugs or news methods of using drugs to treat indicated health conditions. For various reasons,[88] brands apply for patents early in the development and drug approval process, which means that the drug is normally marketed for a period of time much shorter than the full patent term.[89] Although the term of one of the patents covering a particular drug product can be extended to account for FDA regulatory delays, the extension is capped at five years, and in no event can be longer than 14 years from the FDA approval of the NDA.[90]

The FDA requires brand owners to submit information regarding patents covering their approved drugs, which the agency then lists in the so-called Orange Book.[91] The Orange Book embodies a mechanism that provides a critical link between patent and FDA-regulatory aspects of pharmaceuticals.[92] The Hatch-Waxman Act requires generic manufacturers wishing to market a drug under an ANDA to certify to the FDA that either "no relevant patent is listed in the Orange Book" (Paragraph I) or, for each patent that is listed, that the patent has expired (Paragraph II), will expire by the time the generic aims to market the drug (Paragraph III), or is invalid or will not be infringed by the commercialization of the generic drug (Paragraph IV).[93]

For the purposes of this Article, the most interesting paragraph is Paragraph IV. A Paragraph IV certification indicates the generic's wish to market its copy of the branded drug product under an ANDA before the expiration of all the patents listed in the Orange Book as covering the drug, which is possible only if the patent claims are invalid or not infringed by the ANDA-approved product. The filing of a Paragraph IV certification is deemed by statute to be an act of patent infringement that allows the brand to initiate a lawsuit in order to litigate the issue of the generic's liability,[94] which in turn triggers an automatic 30-month stay

[88] *See infra* Part II.
[89] Before approval, pharma companies still have the right under the Patent Act to exclude others from making, using, and selling the invention. *See* 35 U.S.C. §§ 154(d), 271.
[90] *Id.* § 156(g)(6)(A), (c)(3). On various regulatory extensions in the FDA context, see generally Stephanie Bair, *Adjustments, Extensions, Disclaimers, and Continuations: When Do Patent Term Adjustments Make Sense?*, 41 CAP. U. L. REV. 445, 445 (2013).
[91] See U.S. FOOD AND DRUG ADMIN., *Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations*, https://www.accessdata.fda.gov/scripts/cder/ob/default.cfm (last updated Oct. 2017).
[92] On the concept of linkage, see Ron A. Bouchard et al., *Empirical Analysis of Drug Approval-Drug Patenting Linkage for High Value Pharmaceuticals*, 8 NW. J. TECH. & INTELL. PROP. 174 (2010).
[93] § 355(j)(2)(A)(vii)(I)-(IV).
[94] 35 U.S.C. § 271(e)(2)(A).

against the approval of the ANDA.[95] If the generic obtains a judgment of invalidity or noninfringement of the relevant Orange Book-listed patents, it earns permission to market its drug before the patent expiration dates. To encourage patent challenges, the first generic to take on the brand's Orange Book patents is eligible to receive, if certain conditions are met, its own exclusivity that keeps it as the sole additional market entrant for 180 days after the litigation between the patentee and generic concludes.[96]

The stakes of patent litigation built into the Hatch-Waxman regime are high. A finding of no patent infringement liability allows for generic entry and typically leads to dramatically lowered prices of branded drugs and, concomitantly, significantly reduced profit margins for the brand.[97] In particular, a judgment invalidating the patent could be financially devastating for the innovator company unless it has other drugs in the pipeline.[98] A similar result obtains when the patent covering a blockbuster drug expires, a phenomenon aptly described as the "patent cliff."[99] Although branded drugs are nearly always priced higher than generics—even after patent expiration—basic economics dictates that, once patent exclusivity is gone, the innovator company can charge nowhere near the price it did when it was the sole maker of the drug, i.e., while the Orange Book-listed patents were still in effect.[100]

Moreover, once the generics enter, the brand's losses are cemented by so-called "generic substitution" laws,[101] which are in effect in almost every state. Although the details vary by state, the basic aim behind these laws is to have pharmacists fill a prescription with a generic even when the doctor prescribes the more expensive brand, whether out of habit, loyalty, unjustified belief that the brand is somehow better, or for some other reason.[102] In many states, substitution laws take a

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[95] 21 U.S.C. § 355(j)(5)(B)(iii).
[96] 21 U.S.C. § 355(j)(5)(B)(iv); *see* C. Scott Hemphill & Mark A. Lemley, *Earning Exclusivity: Generic Drug Incentives and the Hatch-Waxman Act*, 77 ANTITRUST L.J. 947 (2011).
[97] *See* Susan Decker et al., BLOOMBERG, *Teva's Patent Loss Marks Second Blow in Weeks as New Year Begins*, https://www.bloomberg.com/news/articles/2017-01-30/teva-loses-ruling-invalidating-patents-on-copaxone-drug (Jan. 30, 2017).
[98] *Id.*
[99] *See* Chie Hoon Song & Jeung-Whan Han, *Patent Cliff and Strategic Switch: Exploring Strategic Design Possibilities in the Pharmaceutical Industry*, 5 SPRINGERPLUS 692 (2016); PHARMTECH.COM, *Responding to the Patent Cliff*, http://www.pharmtech.com/responding-patent-cliff (July 1, 2013).
[100] *See* Song & Han, *supra* note 99.
[101] *See supra* notes _-_ and accompanying text.
[102] *See infra* notes _-_ and accompanying text.

permissive form[103]—in other words, the pharmacist may fill a prescription for a brand with a generic—but in some states the switch is mandatory.[104] Although this result seems harsh on the brand, it does reinforce a result contemplated by the Hatch-Waxman scheme—lower drug prices. The idea is that at the expiration of all the brand's valid exclusivities, the innovator has received all the reward that it was due and the public can enjoy cost savings from generics.[105]

Significantly, the states tie the pharmacists' ability to substitute generics for brands to the FDA's determination that the two are "therapeutic equivalents," as brands and generics typically are. This standard requires, among other things, "identical amounts of the same active drug ingredient in the same dosage form and route of administration."[106] One corollary of this requirement is that if, for example, the dosing is different between the two drug products, they are no longer therapeutically equivalent and substitution is therefore not allowed. Returning to this Article's central example of extended- versus immediate-release forms of a drug, one observes that the two are not substitutable because of the difference in dosing. In the drug modification that led to the *Actavis* antitrust case, the immediate-release version was indicated for a twice-a-day 20-milligram dose administration, while the extended-release version was indicated only for one 28-milligram daily dose,[107] rendering the two versions therapeutically distinct. The product-hopping strategy mentioned in the Introduction, then, is born of an interplay between state and federal drug regulatory regimes—but, as we will see in the next Part, is ultimately made possible by patent law. It is to patent law, then, that I now turn.

II. DRUGS, PATENTS, AND PRODUCT CHANGES

A. Pioneering and Secondary Patents

The conventional wisdom has it that patents play a critical role in drug development and, more generally, that chemical and pharmaceutical

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[103] *See, e.g.*, CONN. GEN. STAT. ANN. § 20-619 (West 2017) (permitting generic substitution unless the prescriber or purchaser states otherwise).

[104] *See, e.g.*, FLA. STAT. ANN. § 465.025 (West 2017) (mandating generic substitution unless the prescriber states otherwise).

[105] Interestingly, some insurers and benefit managers have been making side deals with brand companies that would ensure that prescriptions are filled brand rather than generic drugs. *See* Charles Ornstein & Katie Thomas, *Take the Generic, Patients Are Told. Until They Are Not*, N.Y. TIMES (Aug. 6, 2017), https://www.nytimes.com/2017/08/06/health/prescription-drugs-brand-name-generic.html?mcubz=0.

[106] *See* U.S. FOOD AND DRUG ADMIN., *Orange Book Preface*, https://www.fda.gov/Drugs/DevelopmentApprovalProcess/ucm079068.htm.

[107] New York *ex rel.* Schneiderman v. Actavis plc, 787 F.3d 638, 674 (2d Cir. 2015).

patents are the success story of the patent system.[108] Because the pharmaceutical industry is one in which a high amount of upfront investment is required, the drug-maker's ability to recoup it by charging supracompetitive prices made possible by patent exclusivity is critical for preserving incentives for pharmaceutical innovation.[109] Indeed, since many drug candidates fail to make it through the FDA approval process, the brand company's ability to "cash in" on blockbuster drugs that do make it to the market can offset the losses associated with drug candidates that are unsuccessful.[110] While the FDA's five-year "new chemical entity" exclusivity serves as a backstop that provides some reward when no patent can be obtained, by many accounts this period is simply too short to give pharmaceutical companies sufficient return on investment.[111]

New drugs typically represent significant advances in both science and health care, and are frequently protected by strong patents on newly discovered chemical entities.[112] Because the validity of these patents is rarely challenged successfully by generics in Hatch-Waxman litigation, the principal threat to the exclusivity they provide to brand companies entails the passage of time. On the front end, it is the time lost to the process of FDA approval, when the patent clock is ticking but the product cannot yet be marketed.[113] On the back end, it is of course the expiration of the patent.[114] Whether, even with the statutory extensions, useful term length that the brand's pioneering patents currently afford serves as an adequate incentive in the face of long research timelines and regulatory delays is an issue of considerable controversy, and some recent empirical work indicates that the patent term is probably too short,

[108] Mark Schankerman, *How Valuable Is Patent Protection? Estimates by Technology Field*, 29 RAND J. ECON. 77 (1998); Mark Schankerman et al., *Patents and the Global Diffusion of New Drugs*, 106 AM. ECON. REV. 136 (2016); *see also* DAN L. BURK & MARK A. LEMLEY, THE PATENT CRISIS AND HOW THE COURTS CAN SOLVE IT 49-66 (2009).
[109] Grabowski & Vernon, *supra* note 14.
[110] Joseph A. DiMasi et al., *Innovation in the Pharmaceutical Industry: New Estimates of R&D Costs*, 47 J. HEALTH ECON. 20 (2016).
[111] *See, e.g.*, Eric Budish et al., *Do Firms Underinvest in Long-Term Research? Evidence from Cancer Clinical Trials*, 105 AM. ECON. REV. 2044 (2015); Grabowski & Vernon, *supra* note 14; Erika Lietzan, *The Drug Innovation Paradox*, 83 MO. L. REV. (forthcoming 2018), https://ssrn.com/abstract=2948604.
[112] *See* C. Scott Hemphill & Bhaven Sampat, *Drug Patents at the Supreme Court*, 339 SCI. 1386, 1386 (2013). Sometimes, the pioneering patents are directed to methods of use of known compounds. For a well-known example, see Burroughs Wellcome Co. v. Barr Labs., Inc., 40 F.3d 1223 (Fed. Cir. 1994) (upholding the validity of method patents directed to treating HIV-AIDS with a drug called AZT).
[113] Shamnad Basheer, *The Invention of an Investment Incentive for Pharmaceutical Innovation*, 15 J. WORLD INTELL. PROP. (2012); Lietzan, *supra* note 111; Song & Han, *supra* note 99.
[114] Song & Han, *supra* note 99, at 692.

particularly for some difficult-to-develop drugs.[115] Several commentators have, therefore, proposed tying the length of the patent term to R&D expenditures, or at least to the time it takes to get a product to market, so as to preserve incentives for long-term research in particular.[116] Along these lines, one scholar, Professor Erika Lietzan, suggested eliminating the five-year cap on patent term extensions to account for regulatory delays.[117]

Secondary patents are different. Unlike their pioneering counterparts, secondary patents tend to be weaker, and are often invalidated in litigation.[118] Moreover, these patents typically cover a variation of an already-approved drug, which in practice means that the approval of the underlying product generally does not take up nearly as much research and development time as that of the pioneering version.[119] But because it is a foundational principle of patent law that the length of the patent term does not vary depending on the patent's "strength,"[120] even if the strength could be somehow quantifiable, secondary pharmaceutical patents get the term of twenty years from the effective date of application just like all others.[121] Just as pioneering patents, these patents are listed in the Orange Book (for the follow-on formulation) and receive associated FDA-provided benefits, including the requirement of a Paragraph IV certification if the generic wishes to market the new product before patent expiration and an automatic 30-month stay after the litigation commences.[122]

To be sure, the very division of patents into "pioneering" and "secondary" is somewhat arbitrary—a patent is a patent, and it does not issue from the PTO with a "primary" or "secondary" label.[123] In the pharmaceutical space, though, a clear pattern of patenting has emerged

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[115] Budish et al., *supra* note 111; *see also* Benjamin N. Roin, *The Case for Tailoring Patent Awards Based on the Time-to-Market of Inventions*, 61 UCLA L. REV. 672 (2014).
[116] Budish et al., *supra* note 111; Lietzan, *supra* note 111; Mark D. Shtilerman, *Pharmaceutical Inventions: A Proposal for Risk-Sensitive Rewards*, 46 IDEA 337 (2006); *see also* Son Le & Neel U. Sukhatme, *Risk, Return, and Suboptimal Innovation in Pharmaceuticals*, https://cardozo.yu.edu/sites/default/files/Le%20and%20Sukhatme%20Risk%20Return%20and%20Suboptimal%20Innovation%20in%20Pharmaceuticals%208-10-17.pdf.
[117] Erika Lietzan, *The Foundations and Theories of Patent Term Restoration* (on file with author).
[118] *See* Hemphill & Sampat, *supra* note 112.
[119] *See* Himanshu Gupta et al., *Patent Protection Strategies*, 2 J. PHARM. BIOALLIED SCI. 2 (2010).
[120] *See* Robert P. Merges and Richard R. Nelson, *On the Complex Economics of Patent Scope*, 90 COLUM. L. REV. 839 (1990) (questioning this rule).
[121] 35 U.S.C. § 154(a)(2). Such patents, to be sure, do not qualify for regulatory delay extensions under § 156.
[122] *See supra* notes _-_ and accompanying text.
[123] *But cf.* Dmitry Karshtedt, *The Completeness Requirement in Patent Law*, 56 B.C. L. REV. 949 (2015) (proposing a limited patent right for a set of inventions that are currently not patentable).

that makes the labels appropriate as a heuristic matter.[124] A broad patent, often containing claims to a group of chemical compounds that includes the active ingredient of the drug, is duly followed years later by new claims directed to the active ingredient mixed with polymeric carriers, tablets containing the active ingredient that have certain dissolution rates, specific crystalline forms of the active ingredient, and the like. The issue of the new patent is, in turn, accompanied by a product hop. This pattern has appeared time and again: even though the term "product hop" was coined by Professor Herbert Hovenkamp in the previous decade,[125] Dr. Kessler expressed concern about the practice in the 1990s.[126]

For the sake of illustration, let us consider a "simple" patent claim that appeared in an actual secondary patent: "A sustained release formulation comprising a gelling agent and 11–[4–[2–(2–hydroxyethoxy)ethyl]–1–piperazinyl]dibenzo–[b, f] [1, 4] thiazepine or a pharmaceutically acceptable salt thereof, together with one or more pharmaceutically acceptable excipients."[127] The phrase of particular note in this claim is "a gelling agent," whose addition distinguishes this claim from what was done before.[128] The gelling agent makes it possible for the drug containing the active chemical ingredient, a derivative of the so-called "thiazepine" class of chemicals called quetiapine, to function as a "sustained," i.e., extended, release formulation.[129] In contrast, the corresponding primary patent was significantly broader: it claimed the quetiapine recited in the secondary patent as well as related thiazepine compounds, but without the gelling agent, and it was used to provide exclusivity for the marketing of the immediate-release quetiapine formulation.[130] In patent terminology, the two patents have a "genus-species" relationship,[131] whereby the subject matter claimed in the narrower, secondary "gelling agent" patent is a "species" of the various embodiments coverered by the broader, primary "genus" patent claims that lack the "gelling agent" limitation. Significantly, the "extended release" combination of quetiapine and the gelling agent is covered by *both* the primary and the secondary patents. Therefore, third parties are

[124] *See* Hemphill & Sampat, *supra* note 112. The FDA, too, recognizes the difference between "primary and secondary" products via NDA classification codes. *See infra* notes _-_ and accompanying text.
[125] HOVENKAMP ET AL., *supra* note 7.
[126] Kessler, *supra* note 26.
[127] U.S. Patent No. 5,948,437, claim 1 (filed May 28, 1997).
[128] *See* U.S. Pat. No. 4,879,288 (filed Mar. 20, 1987).
[129] *See* AstraZeneca AB v. Anchen Pharm., Inc., Nos. 10-cv-1835, 10-cv-4203, 11-cv-2484 (JAP)(TJB), 10-cv-4205, 10-cv-4971, 10-cv-5519, 11-cv-2483, 2012 WL 1065458 (D.N.J. Mar. 29, 2012), *aff'd*, 498 Fed. App'x 999 (Fed. Cir. 2013) (mem.).
[130] *See id.* at *55.
[131] *See* Rogers, *supra* note 50.

prevented form marketing *either* the extended-release version *or* the immediate-release version of the quetiapine drug during the life of the first patent,[132] but they can market the immediate-release version—though not the extended-release version, unless the second patent is invalidated or adjudged non-infringed—after the first patent expires.

To complete this example with some real-life information on the underlying drug, immediate-release quetiapine was a novel drug type that turned out to be particularly effective for bipolar depression,[133] as well as for other conditions like schizophrenia and psychosis. It took AstraZeneca, the discoverer of quetiapine, over ten years to obtain FDA approval for this drug, which is now marketed under the brand name Seroquel IR (immediate-release).[134] The version with the gelling agent, as the claim indicates, is the "sustained release" form of quetiapine, which was approved in a little over a year from application and marketed as Seroquel XR (extended-release).[135] The extended-release patent from which the representative claim above is drawn expired in 2017, while the pioneering patent on quetiapine expired in 2012. The courts have upheld the validity of the secondary, Seroquel XR patent based principally on the argument that, while drug switches from immediate to extended release have particularly unpredictable effects on the treatment of patients with psychiatric conditions, the switch from IR to XR in this case did not appear to interfere with the efficacy of the drug.[136]

What, then, are the challenges that brand companies face when attempting to obtain a patent on a combination of an active ingredient with, for example, a gelling agent when the active ingredient is already known? And how can the new patent help the brand "extend" exclusivity even though the original patent has expired?[137] I turn to these issues in the sections that follow.

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[132] *See* Merges & Nelson, *supra* note 120 (discussing the concept of so-called "blocking" patents).
[133] *See* Michael E. Thase, *Quetiapine Monotherapy for Bipolar Depression*, 4 NEUROPSYCHIATRIC DISEASE TREATMENT 21 (2008).
[134] *See id.*
[135] *See* U.S. FOOD AND DRUG ADMIN., CENTER FOR DRUG EVALUATION AND RESEARCH, *Approval Package for Application*, NDA 22-047, https://www.accessdata.fda.gov/drugsatfda_docs/nda/2007/022047Orig1s000Approv.pdf.
[136] *See* AstraZeneca AB v. Anchen Pharm., Inc., Nos. 10-cv-1835, 10-cv-4203, 11-cv-2484 (JAP)(TJB), 10-cv-4205, 10-cv-4971, 10-cv-5519, 11-cv-2483, 2012 WL 1065458 (D.N.J. Mar. 29, 2012), *aff'd*, 498 Fed. App'x 999 (Fed. Cir. 2013) (mem.). For a comparative study, see Lars Eriksson et al., *Use of Quetiapine XR and Quetiapine IR in Clinical Practice for Hospitalized Patients with Schizophrenia: A Retrospective Study*, 2 THER. ADV. PSYCHOPHARMACOL. 217 (2012).
[137] To be clear, "extend" is in quotes because the original patent is not actually being extended. *See* Jonathan J. Darrow, *Debunking the Evergreening Patents Myth*, 131 HARV. L. RECORD 6 (2010).

B. Basics of Pharmaceutical Patenting

In order to obtain patent rights, inventors—or, perhaps more commonly, the firms those inventors work for—begin by filing patent applications with the PTO. An application contains one or more claims desired by inventors, such as the illustrative "gelling agent plus quetiapine" claim above. A PTO examiner assesses the claims for compliance with the various requirements of patentability, a typically time-consuming process that involves multiple iterations of arguments between the applicant and the PTO. Frequently, the claims as filed in their initial form are amended during this process. The amendments usually narrow the claims until the examiner's objections to patentability are overcome. If the patent issues, the validity or patentability of the claims can be challenged in a district court—for example, when a Paragraph IV filing by a generic company triggers a patent lawsuit—or in an administrative PTO tribunal called the Patent Trial and Appeal Board (PTAB). In the district courts, where Hatch-Waxman cases are resolved, issued patents enjoy the presumption of validity.[138] In the PTAB, they do not.[139]

Patentability requirements that are particularly relevant to claims on small-molecule drugs and their improvements include novelty, non-obviousness, and utility. Generally speaking, the novelty requirement of 35 U.S.C. § 102 prohibits patents on subject matter that has become part of the public domain, whether via documentary disclosures, prior patenting, public uses of the material that the applicant wishes to patent, or sales of the material.[140] The non-obviousness requirement of § 103, in contrast, essentially bars patents on claims that, while not identically disclosed by prior publications or activities, are so close to what is already known as to be within the grasp of the public domain.[141] Finally, the utility requirement of § 101 states that the subject matter to be patented must be "useful."[142] In the pharmaceutical context, this means that the applicant must adduce some proof that the claimed chemical compound can be potentially effective in treating some health condition.[143] Both in the pharmaceutical space and in other fields, courts have held

[138] 35 U.S.C. § 282(b)(2).
[139] *Id.* § 316(e).
[140] *Id.* § 102(a).
[141] *Id.* § 103(a).
[142] *Id.* § 101.
[143] *See* Brenner v. Manson, 383 U.S. 519 (1966).

emphatically that the utility requirement does not require that the patented invention be in any way better than what is known.[144]

Various features of the novelty, non-obviousness, and utility requirements interact to encourage the filing of patent applications as early as possible in the drug development process.[145] The longer the applicant waits, the more likely it is that various activities the firm engages in while performing research on a new drug will render the claims non-novel, or "anticipated."[146] For example, a clinical trial could force disclosures that constitute patent-barring public use,[147] and a contract between a drug-maker and a distributor could be a patent-barring sale.[148] Patent applicants, to be sure, are entitled to a one-year "grace period" in which to file an application in the PTO after a public use or sale,[149] but this does little to discourage the rush to the Office—in part because the grace period does not exist in some foreign jurisdictions, and pharmaceutical companies are loath to give up these rights if they are seeking a worldwide market for their product.[150] In addition, the longer the delay, the more "prior art" disclosed by third parties accumulates in the world, making it more likely that the claim will be anticipated or rendered obvious.[151]

In the meantime, the utility requirement can be readily satisfied with pre-clinical studies, years before the drug will come up for FDA approval. Indeed, the Court of Appeals for the Federal Circuit, the court with exclusive jurisdiction over patent appeals, made clear that "FDA approval . . . is not a prerequisite for finding a compound useful within the meaning of the patent laws."[152] It explained that "[u]sefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development,"[153] and that "[t]he stage at which an invention in this field becomes useful is well before it is ready to be administered to humans."[154] Accordingly, at least when it comes to pioneering patents,

[144] Lowell v. Lewis, 15 F. Cas. 1018, 1019 (C.C. D. Mass. 1817) (Story, J.); *see* Chao, *supra* note 12.
[145] *See generally* Dmitry Karshtedt, *Did Learned Hand Get It Wrong?: The Questionable Patent Forfeiture Rule of* Metallizing Engineering, 57 VILL. L. REV. 261 (2012).
[146] Sichelman, *supra* note 36.
[147] Dey, LP v. Sunovion Pharm., Inc., 715 F.3d 1351 (Fed. Cir. 2013).
[148] Meds. Co. v. Hospira, Inc., 827 F.3d 1363 (Fed. Cir. 2016) (en banc).
[149] 35 U.S.C. § 102(b).
[150] *See* Robert P. Merges, *Priority and Novelty Under the AIA*, 27 BERKELEY TECH. L.J. 1023, 1032 (2012)
[151] Sean B. Seymore, *Rethinking Novelty in Patent Law*, 60 DUKE L.J. 919 (2011).
[152] *In re* Brana, 51 F.3d 1560, 1568 (Fed. Cir. 1995).
[153] *Id.*
[154] *Id.*

brand companies file their applications early, even though that means years of patent term lost to the FDA approval process. For their part, patent examiners are not generally engaged in the evaluation of clinical data with respect to the claimed drug's safety and efficacy because such data is not required for patentability, and is often unavailable when a patent application is filed.[155]

The pressure to file early, however, is somewhat reduced for secondary patents. While the public use and on-sale bars are still a threat, research and development timelines for follow-on products tend to be shorter and their success in meeting the FDA's requirements of safety and effectiveness, somewhat more predictable. As a result, the timeframe in which a patent-barring event may occur is reduced. More significantly, the best prior art against the claims in the secondary patents will often be the patentee's own disclosures in its own, pioneering patents.[156] Indeed, the brand company is the world's expert in the science behind the blockbuster drug and its variations, and often owns a great deal of undisclosed know-how in addition to the dominant patent that prevents others from making and selling a product that contains the active drug ingredient.[157] Accordingly, third parties face formidable obstacles in developing new versions of the drug that would create prior art against the brand's follow-on patents or threaten its market position with respect to follow-on products.

The challenge for a brand company wishing to obtain a secondary patent, then, is often to overcome its own pioneering patent, and the most significant hurdle it must surmount from the patentability perspective is often the requirement of non-obviousness, codified in § 103 as follows:

> A patent for a claimed invention may not be obtained, notwithstanding that the claimed invention is not identically disclosed as set forth in section 102, if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains.[158]

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[155] *See* Sherkow, *supra* note 44.
[156] *See, e.g.*, Tyco Healthcare Grp. LP v. Mutual Pharm. Co. 642 F.3d 1370 (Fed. Cir. 2011).
[157] *See* Price, *Expired Patents, Trade Secrets, and Stymied Competition*, *supra* note 48. *But cf.* Jonathan J. Darrow, *The Patentability of Enantiomers: Implications for the Pharmaceutical Industry*, 2007 STAN. TECH. L. REV. 2, at *13 (discussing the example of Sepracor, a company specializing in the development of so-called "enantiomer" versions of drugs made by others).
[158] 35 U.S.C. § 103(a).

Given that the term "obvious" is not self-defining, the structure of the § 103 inquiry had to be developed by courts. The so-called *Graham* factors guiding analysis under § 103, set forth in the foundational Supreme Court case of *Graham v. John Deere*, are "the scope and content of the prior art," "differences between the prior art and the claims at issue," and "the level of ordinary skill in the pertinent art."[159] A later Supreme Court case called *KSR v. Teleflex*,[160] as well as further glosses by the Federal Circuit, established that PTO examiners or defendants challenging issued patents as invalid under § 103 often need to show some motivation to combine or modify the prior art to make the claimed invention, and also demonstrate that the patentee would have had a reasonable expectation of success involving the patented subject matter at the time the application was filed.[161]

In addition, courts in the obviousness inquiry consider "[s]uch secondary considerations as commercial success, long felt but unsolved needs, failure of others,"[162] and so on. This evidence, sometimes also called "objective indicia of non-obviousness,"[163] can generally only help the patentee, though establishing its relevancy for a claim's non-obviousness does require a showing of some connection between the evidence and the patented invention.[164] For example, if commercial success is solely attributable to advertising rather than to the technical quality of the improvement over the prior art, then it may not help the applicant show that the claims are non-obvious.[165] Interestingly, the applicant (or patentee defending validity) may successfully argue, for example, that there was long-felt need for a drug modification even when it owned a broad, pioneering patent that could exclude others from practicing that modification and all others.[166] Although, to be sure, the

[159] 383 U.S. 1, 17-18 (1966).
[160] *See* KSR Int'l Co. v. Teleflex Co., 550 U.S. 398 (2007).
[161] *See In re* Stepan Co., 868 F.3d 1342, 1345-46 (Fed. Cir. 2017); *cf.* Arctic Cat Inc. v. Bombardier Recreational Prods. Inc., 876 F.3d 1350 (Fed. Cir. 2017); *see also* American Innotek, Inc. v. United States, 706 Fed. App'x 686, 686 (Fed Cir. 2017) (unpublished) (citing Apple Inc. v. Samsung Elecs. Co., 839 F.3d 1034, 1048 (Fed. Cir. 2016) (en banc) (holding that secondary considerations must be considered in every case where relevant, but can be overcome by other *Graham* factors). To be sure, "unexpected results," such as clinical efficacy, sometimes do find their way into the "prima facie" inquiry under the first three *Graham* factors. *See generally* Mark A. Lemley, *Expecting the Unexpected*, 92 NOTRE DAME L. REV. 1369 (2017).
[162] *Graham*, 383 U.S. at 18.
[163] Stratoflex, Inc. v. Aeroquip Corp., 713 F.2d 1530, 1538-39 (Fed. Cir. 1983).
[164] *See* ClassCo, Inc. v. Apple, Inc., 838 F.3d 1214, 1220 (Fed. Cir. 2016).
[165] *See* Robert P. Merges, *Commercial Success and Patent Standards: Economic Perspectives on Innovation*, 76 CALIF. L. REV. 805, 860 (1988).
[166] Merck Sharpe & Dohme Corp. v. Hospira, Inc., 874 F.3d 724, 1370 (Fed. Cir. 2017) *But cf.* Merck & Co. v. Teva Pharm. USA, Inc., 395 F.3d 1364, 1377 (Fed. Cir. 2005). *See generally* Jonathan J. Darrow, *Secondary Considerations: A Structured Framework for Patent Analysis*, 74 ALBANY L. REV. 47 (2012).

Patent Act shields from infringement activities relating "solely for uses reasonably related to the development and submission of information under a Federal law which regulates the manufacture, use, or sale of drugs,"[167] such as research designed to obtain an ANDA approval or even approval of a new and improved version of the branded drug, it of course does not allow a competitor to actually market a drug product covered by someone else's patent.[168] Thus, it is possible that long-felt need could not be filled largely because of the brand's dominant patent.[169]

Although not completely irrelevant as under the utility requirement, the relative clinical value of the patented product frequently plays only a tangential role in the obviousness inquiry for both legal and institutional reasons. Non-obviousness in the pharmaceutical arts is as much, if not more, concerned with the patent's achievement in the field of chemical technology—triggering, for example, an inquiry whether a particular polymer would be expected to slow the dissolution rate of a particular drug—than with the drug's relative usefulness in medical care.[170] As the Seroquel example suggests, the patentee could, however, sometimes introduce evidence in court or at the PTO tending to show that the drug is unexpectedly effective for the condition it is intended to treat in order to counter the argument that a skilled artisan would have had a reasonable expectation of success in making the drug, or perhaps to bolster its secondary considerations case by, for example, providing data showing that the drug meets a long-felt need.[171]

Nonetheless, secondary considerations are, as the term suggests, sometimes relegated to secondary status and are not weighed heavily, making that information less relevant as compared to the facts developed under the other three *Graham* factors.[172] Moreover, particularly when an applicant attempts to use data to establish patentability at the patent examination stage, it may not be sufficiently robust to speak to clinical effectiveness, even broadly defined,[173] given that the research involving the drug can still then be in the early stages.[174] Finally, applicants

[167] 35 U.S.C. § 271(e)(1).
[168] *See* Momenta Pharm., Inc. v. Amphastar Pharm., Inc., 686 F.3d 1348 (Fed. Cir. 2012).
[169] *Cf.* Galderma Labs., L.P. v. Tolmar, Inc., 737 F.3d 731, 740-41 (Fed. Cir. 2013).
[170] *See, e.g.*, *In re* Kao, 639 F.3d 1057, 1065-67 (Fed. Cir. 2011).
[171] *See* AstraZeneca AB v. Anchen Pharm., Inc., Nos. 10-cv-1835, 10-cv-4203, 11-cv-2484 (JAP)(TJB), 10-cv-4205, 10-cv-4971, 10-cv-5519, 11-cv-2483, 2012 WL 1065458 (D.N.J. Mar. 29, 2012), *aff'd*, 498 Fed. App'x 999 (Fed. Cir. 2013) (mem.).
[172] *See, e.g.*, Intercontinental Great Brands LLC v. Kellogg N. Am. Co., 869 F.3d 1336, 1353 (Fed. Cir. 2017) (Reyna, J., dissenting).
[173] To include, for example, toxicity or even patient compliance.
[174] *See, e.g.*, Abbott Labs. v. Sandoz, Inc., 544 F.3d 1341, 1355-57 (Fed. Cir. 2008); *see also* Apotex Inc. v. UCB, Inc., 763 F.3d 1354, 1359 (Fed. Cir. 2014) ("The court noted that each

sometimes submit data from a study specifically designed to convince the examiner of the invention's merit, but that does not actually speak to a drug's relative or even absolute effectiveness in any way. But examiners, not trained to analyze studies for scientific rigor in the way that FDA scientists are, might miss what is happening.

This particular strategy is best illustrated by an example of one of the patents that has triggered *New York ex rel. Schneiderman v. Actavis plc*,[175] the antitrust case mentioned in the Introduction and one to which I will return in the next Part as well. Forest Laboratories, which a few years ago became a wholly-owned subsidiary of Actavis, had marketed an Alzheimer's drug called memantine hydrochloride (or simply memantine), under brand name Namenda IR, covered by a patent it had exclusively licensed from another company.[176] One of the pioneering patents, U.S. Patent No. 5,061,703 (the '703 patent), was listed in the Orange Book and included claims to "a method for the prevention or treatment of cerebral ischemia comprising the step of administering, to a patient in need thereof"[177] memantine and other, closely related chemical compounds.

A few years before the expiration of the '703 patent, Forest filed for, and eventually obtained, additional patents related to memantine. These patents cover a drug called Namenda XR for which Forest, and then Actavis, has ultimately obtained approval for and currently markets. Among others, Forest was granted claims that were essentially directed to the pharmacokinetics—or rates of dissolution and absorption—of memantine in the human body. A claim in one of these new patents was directed to a "method for treating Alzheimer's disease comprising once daily administration of a modified release solid oral dosage form" (i.e., a tablet) that included an approximately 28-milligram (mg) dose of memantine and a

> pharmaceutically acceptable polymeric carrier substantially contributing to the modification of the release of the memantine or pharmaceutically acceptable salt thereof, said dosage form sustaining release of the memantine or pharmaceutically acceptable salt thereof

example [in the patent is written in the past tense as if it had occurred, but Dr. Sherman admitted at trial that the experiments were made up in his head.").

[175] 787 F.3d 638 (2d Cir. 2015).

[176] *See* New York v. Actavis plc, No. 14 Civ. 7473, 2014 WL 7015198, at *10 (S.D.N.Y. Dec. 11, 2014).

[177] *See* '703 patent (filed Apr. 11, 1990), claim 1. This particular example has the feature that both the pioneering and secondary patents are method patents rather than patents to drug compositions, but that does not materially affect the analysis here.

> from about 4 hours to about 24 hours following entry of said form into a use environment, wherein said dosage form has a single phase dissolution rate of less than about 80% after passage of about 6 hours following said entry into said use environment.[178]

Although it is much more complicated than the quetiapine "gelling agent" claim above, the concept behind this claim is similar. The idea is—as the "extended release" phrase suggests—that these patents basically claim delayed bioavailability of the active pharmaceutical ingredient, though focusing on actual dissolution rates. The first representative claim includes a "polymeric carrier," which—like a gelling agent—controls the release of memantine in the "use environment," i.e., the human body, by metering the rate of the tablet's dissolution over the time periods recited in the claim. Notably, the claim also includes a "once daily administration" limitation.

Claims covering extended-release versions of drugs drawn to rates of dissolution, and similar formats, are common and sometimes use well-established dissolution-slowing technology combined with the already-known active ingredient.[179] Because of these features, such claims are frequently challenged on the grounds of obviousness.[180] In this case, the PTO examiner accordingly rejected proposed claims reciting "a modified release solid dosage form" of memantine without the once-daily administration limitation as obvious over the prior art, some of it Forest's, that disclosed IR memantine formulations in various dosages—as well as another reference describing "sustained" release formulations of closely related drug compounds.[181] The Examiner concluded that, because the prior art taught both using memantine for the treatment for moderate to severe Alzheimer's and explained how to make extended-release formulations of similar molecules, the publications in totality suggested

[178] U.S. Pat. No. 8,039,009 (filed June 16, 2005) ('009 patent), claim 1. A different set of patents protecting Namenda XR has been invalidated for violating the definiteness requirement of patentability, 35 U.S.C. § 112(b). *See* Forest Labs., Inc. v. Teva Pharm. USA Inc., C.A. No. 14-121-LPS, 2016 WL 54910 (D. Del. Jan. 5, 2016), *aff'd*, Nos. 16-2550, 16-2553, 2017 WL 6311688 (Fed. Cir. Dec. 11, 2016) (unpublished). Forest had licensed this second group of patents from another company, Adamas Pharmaceuticals, pursuant to a joint venture agreement.

[179] *See, e.g.*, Dan-Feng Mei et al., *Formulation Patents and Dermatology and Obviousness*, 3 PHARMACEUTICS 914 (2011); Charles J. Betlach et al., *Bioavailability and Pharmacokinetics of a New Sustained-Release Potassium Chloride Tablet*, 4 PHARM. RES. 409 (1987).

[180] *See* Hemphill & Sampat, *supra* note 45.

[181] U.S. Pat. App. No. 11/155,330, Non-Final Rejection, at 3 (filed Nov. 1, 2010).

the "practice of the instantly claimed invention with a reasonable expectation of success."[182]

The applicant countered that none of the cited references disclosed the specific dissolution rates recited in the claims, nor established that *extended*-release formulations would be useful for the treatment of Alzheimer's.[183] Specifically, the applicant noted that the references would not "lead one skilled in the art to use a modified [i.e., extended] release dosage form comprising about 28 mg of memantine,"[184] and also pointed to a declaration averring that "28 mg memantine modified release dosage forms are surprisingly and unexpectedly effective for the treatment of Alzheimer's disease."[185] In support, the applicant cited a Federal Circuit case holding that "substantially improved results" can point toward non-obviousness.[186] Nonetheless, that case required substantial improvement *over the closest prior art*, which in this case was the IR version of the drug, while the declaration stated that "28 mg memantine modified release was statistically significantly superior *to placebo*."[187] The examiner accordingly maintained the rejection.[188]

The applicant, then, responded with a claim amendment and an argument pointing to a new declaration. The amendment added the phrase "once daily administration," which changed the claims to what became their final form of a method "for treating Alzheimer's disease comprising *once daily administration* of a modified release solid oral dosage form."[189] In the argument, the applicant advanced the theory that the new declaration showed that the "28 mg memantine modified release dosage forms are surprisingly and unexpectedly effective for the treatment of Alzheimer's disease."[190] The declaration pointed to new data showing that 20 mg memantine *as <u>immediate</u> release tablets given once daily to patients* provided little benefit over placebo, while 28 mg memantine *as <u>extended</u> release tablets given once daily to patients* had some benefit in

[182] *Id.*
[183] U.S. Pat. App. No. 11/155,330, Response to Office Action, at 7 (filed Dec. 10, 2010).
[184] *Id.* at 7-8.
[185] *Id.* at 8.
[186] *Id.* (quoting *In re* Soni, 54 F.3d 746, 751 (Fed. Cir. 1995)).
[187] *Id.* The examiner had previously rejected that argument. U.S. Pat. App. No. 11/155,330, Non-Final Rejection, at 3 (filed June 10, 2010).
[188] U.S. Pat. App. No. 11/155,330, Final Rejection (filed Mar. 10, 2011).
[189] U.S. Pat. App. No. 11/155,330, Response to Final Office Action at 2 (filed Mar. 15, 2011) (emphasis added).
[190] *Id.* at 7.

treating Alzheimer's.[191] This, argued the applicant, was a surprising result.

This result, however, should not have really been a big surprise because the FDA had approved IR memantine for a *twice-daily* administration (as two 10 mg tablets).[192] One tablet of IR a day was not going to work, and the right basis for comparison was the drug that Forest had already marketed, not a made-up once-daily regime with the IR version of the drug. Indeed, if only one tablet of IR a day were sufficient to treat Alzheimer's, that would mean that patients have been needlessly taking an extra tablet of Namenda every day. Nonetheless, this argument, coupled with the aforementioned amendment adding "once daily administration," sufficed to overcome the rejection.

This patent, which is dubious at best, has kept generic companies wishing to market their copies of Namenda XR off the market. Generics did contest the validity of Namenda XR patents as part of their Paragraph IV certification,[193] but the case settled early in litigation without the adjudication of validity.[194] Perhaps more significantly, this secondary patent enabled Actavis to carry out a strategy that got in the way of generics' marketing the *original*, IR version after the pioneering patent expired. I now turn to the specifics of this strategy.

C. Product Hopping

1. Characterizing the Patent Cliff

As noted in Part I, brand companies fear the so-called "patent cliff"—the term that refers to the expiration, or perhaps invalidation, of a pioneering patent covering a blockbuster drug. One option for dealing with it is radical innovation—bringing a completely new product to

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[191] *Id.*

[192] *See* U.S. FOOD AND DRUG ADMIN., CENTER FOR DRUG EVALUATION AND RESEARCH, *Approval Package for Application*, NDA 21-487, https://www.accessdata.fda.gov/drugsatfda_docs/nda/2003/21-487_Namenda_Approv.pdf.

[193] Answer to Amended Complaint at 36, Forest Labs. v. Amneal Pharm. LLC, Case No. 1:15-cv-00756 (D. Del. Aug. 5, 2016), ECF No. 90.

[194] Stipulation and Order, Forest Labs. v. Amneal Pharm. LLC, Case No. 1:15-cv-00756 (D. Del. Aug. 31, 2016), ECF No. 102. Under the settlement, if the FDA approves Amneal's ANDA, Amneal may launch its generic product on Jan. 1, 2025. *Id.*; *see also* Carly Helfand, FIERCEPHARMA, *Allergan Sews up a Namenda XR Cushion with Amneal patent settlement* (Sep. 10, 2015), http://www.fiercepharma.com/sales-and-marketing/allergan-sews-up-a-namenda-xr-cushion-amneal-patent-settlement (describing a settlement with another defendant in this case). Such settlements have sometimes been challenged on antitrust grounds. *See* Fed. Trade Comm'n v. Actavis, Inc. 570 U.S. 136 (2013).

market that is supported by FDA and patent exclusivities.[195] This strategy would give the brand a new source of protected revenue at the same time as generic entry reduces the brand's revenue from the previous product.[196] Of course, bringing a completely new drug product to market is easier said than done. Blockbuster drugs, and new chemical-entity drugs generally, require a great deal of investment, cutting-edge research, and luck as the brand works to prove safety and effectiveness to the FDA, a process that may take many years.[197]

Several other strategies, instead involving the brand's attempts to get as much as possible out of a product for which the pioneering patents are expiring, are also available. Providing a taxonomy, Professors Chie Hoon Song and Jeung-Whan Han explain that such strategies include innovation, prevention, extraction, and adaption.[198] Although bright lines between these forms of value-extension are difficult to draw, the categorization is helpful in terms of introducing the landscape of incremental drug changes. According to these authors, innovation strategies include finding new uses for old drugs and, more significantly, "the introduction of a follow-on product, which is either therapeutically or technologically innovative and permits better patient outcomes."[199]

Song and Han apparently contrast this strategy with a "prevention strategy," which involves adding patent coverage without an actual product improvement. Two of the examples they provide are "crystalline forms of the original compound" and "formulations."[200] The contradistinction with "therapeutically or technologically innovative" products is odd because it is certainly possible for a new crystalline form or a new formulation to constitute both a therapeutic and a technological advance, and even a significant one, over the previous version of the drug. But not always, and what would give the medical community some idea whether there is some improvement, or at least some differentiation from the previous version of the product, is data. I will return to this issue in Parts III and IV.

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[195] *See* Song & Han, *supra* note 99, at 693, 704. If this strategy results in a new chemical entity, it nearly always leads to a patent for the brand. *See, e.g.*, Naomi Kresge, BLOOMBERG, *Roche CEO Faces Patent Cliff with Confidence Thanks to New Drugs* (Apr. 27, 2017), https://www.bloomberg.com/news/articles/2017-04-27/roche-quarterly-sales-rise-4-on-new-drugs-as-competition-looms.
[196] *See* Song & Han, *supra* note 99, at 693, 704.
[197] *See supra* notes _-_ and accompanying text.
[198] Song & Han, *supra* note 99, at 698.
[199] *Id.* at 700.
[200] *Id.* at 698.

Finally, Song and Han discuss extraction and adaption strategies. By extraction, the authors mean getting as much value as possible out of the original product even as it falls off the patent cliff. This strategy might, for example, include aggressive marketing efforts directed at doctors[201]—though perhaps, even if successful, those efforts might be blunted by generic substitution laws.[202] Finally, adaption, a "can't beat them, join them" approach, could include a brand's creation of a subsidiary company that makes a so-called "authorized generic" product.[203] As with radical innovation, I will put these two strategies to one side, and focus on the rather common product-hop approach, which could constitute either prevention or innovation. As the Namenda example demonstrates, product changes coupled with acquisition of secondary patents can sometimes constitute prevention, with the follow-on products having dubious therapeutic value over what is already known. Although the facts of Namenda are fairly aggressive, prevention strategies achieved through product hops are not unusual.[204]

2. Namenda—the Rest of the Story

The secondary patent on Namenda XR, discussed in Section B, issued in 2011 and Forest obtained FDA approval of the XR product shortly thereafter. Meanwhile, the pioneering patent that enabled Forest's exclusive marketing of the IR formulation was set to expire in 2015. In 2013, two years before the patent cliff, Forest attempted a "'soft switch,' [to the XR product,] which means that it aggressively marketed Namenda XR to doctors, patients, and pharmacists, and sold XR at a discount that

[201] *Id.* at 699-700. *Cf.* Gideon Parchomovsky & Peter Siegelman, *Towards an Integrated Theory of Intellectual Property*, 88 VA. L. REV. 1455 (2002); Hazel V. Moir & Luigi Palombi, *Patents and Trademarks: Empirical Evidence on Evergreening from Australia*, https://papers.ssrn.com/abstract=2365786; *see also* Note, *Trademarks and "Look-Alike" Drugs*, 15 IND. L. REV. 733, 743-44 & n.58 (1982) ("Because of the nature of research within the drug industry, the innovator manufacturer is often the only source of information regarding the uses and precautions, as well as the physical and pharmacological properties of a new drug. Therefore, physicians and pharmacists rely heavily upon the manufacturers, especially for initial information and clinical studies pertaining to the new drug." (citing DRUG DEVELOPMENT AND MARKETING 124, 182-86 (R. Helms ed. 1975)). For further discussion of drug marketing and advertising, *see infra* notes _-_ and accompanying text.

[202] *See supra* notes _-_ and accompanying text.

[203] Song & Han, *supra* note 99, at 703-04; *see* Thomas Chen, *Authorized Generics: A Prescription for Hatch-Waxman Reform*, 93 VA. L. REV. 459 (2017); Christopher S. Ponder, Note, *The Dubious Value of Hatch-Waxman Exclusivity*, 45 HOUS. L. REV. 555 (2008).

[204] *See, e.g.*, *In re* Suboxone (Buprenorphine Hydrochloride and Naloxone) Antitrust Litig., MDL No. 2445, 2017 WL 4910673, at *11 (E.D. Pa. Oct. 30, 2017).

made it less expensive than IR,"[205] while it also stopped promoting IR.[206] To recap, the strategic reason for the switch concerned the effect of the state generic substitution laws: if physicians continue to prescribe Namenda IR, substitution *is* possible once generics enter after the expiration of the pioneering patent. But if physicians switch to XR, substitution with a generic IR is not possible because IR and XR are not therapeutically equivalent—and generics, then, would have to convince doctors to switch back to IR.[207] As noted bluntly in one commentary, "[a] product hop prevents generic drugs from benefiting from the state substitution laws."[208] To complete the picture, secondary patent coverage prevents generics from marketing XR, for which a separate Paragraph IV certification is required.

The gravamen of Forest's marketing strategy for XR appeared to be patient compliance benefits, as Forest maintained that patients, caregivers and healthcare providers responded favorably to the advantages of the once-daily dosing of the Namenda XR product.[209] But while the marketing worked to some extent, Forest determined that it would not be able to achieve en masse switches.[210] Thus, "after concluding that the 'soft switch' would induce only about 30 percent of Namenda IR users to switch to the new drug before generic entry, Forest announced in February 2014 that [it] would soon discontinue the older drug—what became known as the 'hard switch.'"[211]

At this point, the New York Attorney General got involved, commencing an action against Forest/Actavis under federal antitrust law and related state law claims. Among other things, the Attorney General asserted that Forest violated § 2 of the Sherman Act, which prohibits monopolization or attempted monopolization by a single firm.[212] In the

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[205] *Pharmaceutical Antitrust Update: Courts Address How and When Product Hopping May Violate the Antitrust Laws*, HAUG PARTNERS (Mar. 29, 2017), http://www.haugpartners.com/article/pharmaceutical-antitrust-update-courts-address-how-and-when-product-hopping-may-violate-the-antirust-laws.

[206] *See* New York *ex rel.* Schneiderman v. Actavis plc, 787 F.3d 638, 647-48 (2d Cir. 2015).

[207] *See supra* notes _-_ and accompanying text.

[208] *Pharmaceutical Antitrust Update*, *supra* note 205.

[209] Emily Wasserman, *Forest Laboratories Announces Intention to Continue Marketing Both Namenda® Tablets and Once-Daily Namenda XR® Into the Fall of 2014*, FIERCEPHARMA, (June 11, 2014), http://www.fiercepharma.com/marketing/forest-laboratories-announces-intention-to-continue-marketing-both-namenda%C2%AE-tablets-and ("The Company noted that patient and caregiver response to the NAMENDA XR® product has been exceptionally positive, with caregivers and physicians clearly recognizing the benefits of the single daily dosing regimen.").

[210] *Actavis*, 787 F.3d at 648-49.

[211] Joel Mitnick et al., *Second Circuit Holds "Product Hopping" May Violate Antitrust Laws*, NEW YORK L.J. (July 13, 2015), https://www.sidley.com/-/media/publications/second-circuit-holds-producthopping-may-violate-antitrust-laws.pdf.

[212] *See* 15 U.S.C. § 2.

complaint, the Attorney General laid out what is perhaps the central problem in some product-hopping cases:

> Sometimes, these follow-on drugs may be truly better than the original drug. In other instances, the new versions of the drugs offer little to no therapeutic advantage over the prior versions, and the reformulation of the drug is merely an attempt to game the regulatory system and interfere with effective price competition between branded and generic drugs. Efforts to switch patients to a follow-on drug with little to no clinical benefit solely for the purpose of interfering with generic competition and extending the monopoly life of a drug franchise is sometimes referred to as "product hopping."[213]

New York eventually prevailed on the § 2 claim, obtaining an affirmance of the district court's preliminary injunction ordering Actavis to continue selling Namenda IR. In concluding that Forest violated the Sherman Act, the Court of Appeals for the Second Circuit focused largely on the "consumer coercion" involved in the "forced" switching from IR to XR prior to generic entry, noting that it was unrealistic to expect doctors to return to IR—which generics could make available after the pioneering patents expired—after their patients had to be switched to XR.[214] But on the crucial question of whether XR was actually better for patients, or at least different, the court initially appeared to punt. It noted that "[w]hether XR is superior to IR is not significant in this case" because "[w]hen there is coercion, the technological desirability of the product change bears on the question of monopolistic intent, rather than the permissibility of the defendant's conduct."[215] And here, intent was not in question—record evidence made clear that the defendants engineered the switch with the culpable mindset of avoiding competition.[216]

In determining whether there was an antitrust violation, the court nonetheless had to consider product quality because, once a plaintiff establishes that the defendant engaged in exclusionary conduct, the latter can still escape liability by showing that the conduct had non-pretextual procompetitive justifications, and "[t]he plaintiff may then either rebut those justifications or demonstrate that the anticompetitive harm out-

[213] Complaint, New York v. Actavis plc, No. 14 Civ. 7473, 2014 WL 7015198 (S.D.N.Y. Dec. 11, 2014), ECF. No. 1, *available at* https://assets.documentcloud.org/documents/1385610/5caae9b145.txt
[214] *Actavis*, 787 F.3d at 656 & n.31.
[215] *Id.* at 653 n.25 (citation and alternations omitted).
[216] *Id*. at 658.

weighs the procompetitive benefit."[217] The court, therefore, returned to the point that Forest's internal documents made clear that the switch was pretextual, but then engaged in some balancing. In doing so, the court faulted Forest for "withdrawing a successful drug from the market and introducing a reformulated version of that drug, which has the dual effect of forcing patients to switch to the new version and impeding generic competition, *without a legitimate business justification*."[218] Given this language, one is left with the impression that the case could have well come out differently, even in spite of the "hard switch," had Forest managed to differentiate IR and XR.[219] In internal documents and in subsequent antitrust litigation, Forest could have then focused on the relative qualities of the two products instead of getting called out for its switching strategy, and the alleged pro-competitive justifications would then have not have then been pretextual.

In this case, though, the data that could have bailed Forest out was simply unavailable. To be sure, in the course of safety and effectiveness studies needed to obtain approval for Namenda XR, Forest established that the so-called peak serum concentration of memantine from the proposed dose of XR was 1.5 times greater than that from the approved dose of IR.[220] But that comparison was only a shortcut to showing that XR was safe based on the proxy of high IR doses, giving the same peak serum concentration as the proposed XR dosage, that have been successfully tested for safety.[221] At the time of the attempted switch, there was "no study addressing the comparative efficacy of IR and XR,"[222] and

[217] *Id.* at 652.

[218] *Id.* at 659 (emphasis added). Before finding an antitrust violation, the court had to determine the all-important issue off the relevant market, which it concluded to be memantine. *Id.* at 646-52; *see* Gregory Dolin, *Do Patent Challenges Reduce Consumer Welfare?*, 83 U. CHI. L. REV. ONLINE 256, 262-63 (2017). *But cf.* Mylan Pharm. Inc. v. Warner-Chilcott PLC, 838 F.3d 421 (3d Cir. 2016) (finding no monopolization where there were other drugs available in the relevant market and, since the defendant had no dominant position with the respect to the product at issue, no antitrust violation).

[219] *Cf.* Carlton, *supra* note 61, at 495 (noting the theory that "a pharmaceutical manufacturer of a brand name drug can violate the antitrust laws by introducing a new product that reduces demand for rival legacy generic therapies and offers consumers no significant incremental therapeutic benefits over these legacy products").

[220] *See* U.S. FOOD AND DRUG ADMIN., CENTER FOR DRUG EVALUATION AND RESEARCH, *Summary Review* at 3-4, NDA 22-525, https://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022525Orig1s000SumR.pdf.

[221] *See id.* In addition, the sponsor did present some food effect data, but only with respect to lack of effect of food on bioavailability of memantine as opposed to relative efficacy of XR versus IR. U.S. FOOD AND DRUG ADMIN., CENTER FOR DRUG EVALUATION AND RESEARCH, *Medical Review(s)* at 8, 89. Pharmacokinetics data mirroring that submitted to the FDA was also described in the patents covering Namenda XR. *See* '009 patent, col. 14 l. 60 – col. 20 l. 7.

[222] *Dosing for Patients Currently Taking Namenda*, NAMENDAXR, http://www.namendaxrhcp.com/patients-currently-taking-namenda.aspx (last visited Dec. 9, 2017).

specifically "the clinical impact of [XR's distinct] pharmacokinetic properties is not known since it has not been studied in clinical trials."[223] Moreover, one later study found that the evidence for the claim that switching to a once daily regimen in a related therapy involving a combination of memantine with another drug would "increase treatment adherence and persistence is conflicting, meaning that the added cost of switching patients from generic options . . . may not always be justified."[224] Setting aside the issue of antitrust liability, it would seem that some data on relative benefits of XR and IR could be useful, even crucial, for patients, physicians, payers, and others. But, as exemplified by the Namenda case, relevant data that could differentiate related drug products can sometimes be difficult to come by, and data that has been evaluated by the FDA, even more so. The next Part explains why this is a problem.

III. DRUG MARKETING, THE CASE FOR MORE DATA, AND THE FDA'S ROLE

A. Drug Marketing and Its Role in the Namenda Switch

The relationship between the FDAs' pre-marketing drug approval and the advertising of drugs by brand companies has always been somewhat uneasy. When the FDA determines that a drug product meets the statutory requirements of safety and effectiveness,[225] the approval extends to a particular indication—that is, a specific condition that the drug has been demonstrated to treat, dosing schedule, perhaps a particular age group, and other specifications.[226] The brand is required to include

[223] William James Deardorff & George T. Grossberg, *A Fixed-Dose Combination of Memantine Extended-Release and Donepezil in the Treatment of Moderate-to-Severe Alzheimer's Disease*, 10 DRUG DESIGN, DEV. THER. 3267, 3276 (2016).

[224] *Id.* at 3267; *see also id.* at 3276. This article also makes clear that "[o]ne economic analysis that has not been performed is the comparison of memantine ER and memantine IR in combination with [other drugs] since no studies have been performed comparing the two drugs." *Id.* at 3276.

[225] *See* 21 U.S.C. § 355(b). The precise requirement with respect to new drugs includes "full reports of investigations which have been made to show whether or not such drug is safe for use and whether such drug is effective in use." *id.* § 355(b)(1)(A), though one statutory section uses the actual "safe and effective" language, *id.* § 393(b)(2)(B). Nonetheless, literature distinguishes efficacy, which refers to "the effect of the treatment under optimal conditions," i.e., in the course of clinical trials, from effectiveness, which refers to "the effect of the treatment in routine clinical practice." Cong. Research Serv., RL34208, *Comparative Clinical Effectiveness and Cost-Effectiveness Research: Background, History, and Overview* 4 (2007). Nonetheless, pre-approval studies can, subject to various qualifications based on limitations of such studies, be proxies for effectiveness in actual clinical practice. *Cf. generally* Barbara J. Evans, *Seven Pillars of a New Evidentiary Paradigm: The Food, Drug, and Cosmetic Act Enters the Genomic Era*, 85 NOTRE DAME L. REV. 419 (2010).

[226] 21 U.S.C. § 355 (b)(1)(A); *see* Nathan Cortez, *The Statutory Case Against Off-Label Promotion*, 83 U. CHI. L. REV. ONLINE 124, 124 (2017).

this information on the label, which is a package insert accompanying the drug.[227] Professor Erika Lietzan aptly characterized the FDA's approval and labeling requirements as follows:

> Preapproval does not ensure that new drugs are "safe" and "effective" in an absolute sense. Instead it ensures that the power to make judgment calls about relative risks and benefits at the population level is concentrated in one decisionmaker, it ensures that claims about individual products are supported by data that meet a particular evidentiary standard, and it ensures that the government maintains control over the words used by firms to describe those data.[228]

Notably, the FDA's control over the label does not extend to physician prescribing decisions. Physicians are legally allowed to prescribe drugs for so-called off-label uses and frequently do so when, for example, some evidence exists that this may be a proper course of treatment.[229] Nonetheless, if pharmaceutical companies decide to promote off-label uses, their officers and employees risk liability for introducing a "misbranded" drug into interstate commerce, a misdemeanor violation of the FDCA.[230] The reach of these criminal provisions is, however, in turn limited by the First Amendment. The Second Circuit, for example, held in *United States v. Caronia* that a pharmaceutical company's salesperson could not be constitutionally convicted of truthful and non-misleading promotion of an FDA-approved drug for an off-label use.[231]

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[227] 21 U.S.C. § 353.

[228] Lietzan, *supra* note 117.

[229] *See generally* Coleen Klasmeier & Martin H. Redish, *Off-label Prescription Advertising, the FDA and the First Amendment: A Study in the Values of Commercial Speech Protection*, 37 AM. J. LAW. MED. 315 (2011). *But see* Randall S. Stafford, *Regulating Off-Label Drug Use—Rethinking the Role of the FDA*, 358 NEW ENG. J. MED. 1427, 1427 (2008) ("Although off-label prescribing—the prescription of a medication in a manner different from that approved by the FDA—is legal and common, it is often done in the absence of adequate supporting data.").

[230] 21 U.S.C. § 331(a). The FDA has argued that such promotion is evidence of misbranding. *See* Brief and Special Appendix for the United States at 51, United States v. Caronia, 403 F.3d 149 (2d Cir. 2012), 2010 WL 6351497, *51; *see also* Cortez, *supra* note 226, at 126.

[231] 403 F.3d 149 (2d Cir. 2012). For a discussion of possible implications of *Caronia* for FDA approval practices, see Patricia J. Zettler, *The Indirect Consequences of Expanded Off-Label Promotion*, 78 OHIO ST. L.J. (forthcoming 2018), https://ssrn.com/abstracts=3029621; see also Alan Bennett et al., *Back to First Principles: A New Model for the Regulation of Drug Promotion*, 2 J.L. & BIOSCI. 168, 170 (2015); Christopher Robertson, *When Truth Cannot Be Presumed: The Regulation of Drug Promotion Under an Expanding First Amendment*, 94 B.U. L. REV. 545, 554-55 (2014).

Like general drug promotion, comparative drug advertising is subject to the statutory prohibition "of labeling [that] is false or misleading in any particular."[232] FDA regulations interpreting this and related provisions specifically forbid "drug comparison that represents or suggests that a drug is safer or more effective than another drug in some particular when it has not been demonstrated to be safer or more effective in such particular by substantial evidence or substantial clinical experience."[233] By its terms, this regulation does not prohibit non-comparative advertising, or even comparative advertising that does not address safety or efficacy. Thus, Forest's ad campaign touting Namenda XR without claiming superiority to IR, conducted through both direct-to-consumer television spots[234] and multi-page spreads in medical trade journals,[235] was perfectly lawful. In addition, it was no violation of statute or FDA regulation for Forest, and later Actavis, to make statements in press releases like the following: "[P]atient and caregiver response to the NAMENDA XR® product has been exceptionally positive, with caregivers and physicians clearly recognizing the benefits of the single daily dosing regimen."[236]

Such advertisements and statements, while not affirmatively misleading or otherwise illegal, do not tell the whole story. For example, it may well be accurate that some caregivers like Namenda XR, perhaps unjustifiably,[237] because of a relatively small number of doses to be

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[232] 21 U.S.C. § 352 (a)(1). False Claims Act liability is possible in these scenarios as well.

[233] 21 C.F.R. § 202.1(e)(6)(ii) (2008). Comparative advertising between drug forms both of which are on the market from situations when the FDA has withdrawn the original version of the drug, usually for safety reasons. *See, e.g.*, *Determination that the OXYCONTIN (Oxycodone Hydrochloride Drug Products Covered by New Drug Application 20-553 Were Withdrawn from Sale for Reasons of Safety or Effectiveness*, 78 Fed. Reg. 23273, 23274 (Apr. 18, 2013) ("Original OxyContin has the same therapeutic benefits as reformulated OxyContin. Original OxyContin, however, poses an increased potential for abuse by certain routes of administration, when compared to reformulated OxyContin. Based on the totality of the data and information available to the Agency at this time, FDA concludes that the benefits of original OxyContin no longer outweigh its risks."). I thank Professor Patricia Zettler for suggesting that I make this point.

[234] See *Namenda XR TV Commercial, "Be a Guardian,"* ISPOT.TV, https://www.ispot.tv/ad/7F3x/namenda-xr-be-a-guardian. Empirical work has shown that patient demand can drive prescribing decisions. *See* Rebecca K. Schwartz et al., *Physician Motivations for Nonscientific Drug Prescribing*, 28 SOC. SCI. MED. 577, 579 (1989) ("Patient demand was the most commonly cited motivation for prescribing the target drugs . . . ."); *see also* Andrea Coscelli, *The Importance of Doctors' and Patients' Preferences in the Prescription Decision*, 48 J. INDUSTR. ECON. 349 (2000); Ramkumar Janakiraman, *Physicians' Persistence and Its Implications for Their Response to Promotion of Prescription Drugs*, 54 MGMT. SCI. 1080 (2008).

[235] *See* DRUG TOPICS 2-4 (Aug. 2013), http://images2.advanstar.com/pixelmags/drug-topics/pdf/2013-08.pdf.

[236] Wasserman, *supra* note 209; *see* United States v. Harkonen, No. C 08–00164 MHP, 2009 WL 1578712 (N.D. Cal. June 4, 2009) (finding a press release to constitute a form of drug labeling); *see also* Cortez, *supra* note 226, at 129.

[237] *See* Deardorff & Grossberg, *supra* note 223.

administered to patients, but busy physicians[238] might not closely scrutinize the claim and erroneously come to believe that XR has replaced IR as the standard of care.[239] The print ad, to be sure, stated that "[t]here is no study addressing the comparative efficacy" of Namenda XR and IR, but medical care providers do not always notice these disclaimers.[240] For example, a recent study found that only 44.9% of the physicians surveyed in a study of perceptions of a print ad suggesting an "alternative" treatment noticed the "context statement"[241] declaring that "[t]he products in this comparison may or may not be equally effective or safe,"[242] while a significantly larger percentage, 76%, noticed the price comparison that the advertiser intended for them to notice. The study's authors concluded that "[t]he context statement did not affect evaluations of the price-comparison claim's importance or accuracy and did not have the intended effects on perceptions of uncertainty about drug interchangeability."[243] Indeed, "a realistic context statement to a physician-targeted prescription drug ad did not generate sufficient awareness of claim caveats to differentiate price-comparison response of those exposed to the context statement from those who were not."[244] Another study showed that journal advertisements and other forms of marketing have a greater effect on physician prescribing decisions than evidence in scientific articles.[245] These findings are consistent with broader claims that so-called "schemas," or biases, and other cognitive

[238] *See, e.g.*, Cynthia M. Ho, *First Amendment Overprotection of Alternative Facts: Cognitive Biases Behind Pharmaceutical Mis-Marketing* (on file with author).

[239] *Cf.* Sheely v. Memorial Hosp., 710 A.2d 161, 166-67 (R.I. 1998) (holding that the standard of care in medical malpractice cases is determined by national custom); *see* Arti K. Rai, *The Information Revolution Reaches Pharmaceuticals: Balancing Innovation, Incentives, Cost, and Access in the Post-Genomics Era*, 2001 U. ILL. L. REV. 173, 207 ("[P]hysicians, and plans, that deliver care in a parsimonious fashion may be deemed to deviate from the custom-based standard of care and may, on that basis, be held liable in tort."); *see also* Bloche, *supra* note 73, at 464 ("If there are multiple therapeutic options and the one chosen turns out badly, the plaintiff can find a physician-expert witness who would have opted for one of the other options."); Richard S. Saver, *Health Care Reform's Wild Card: The Uncertain Effectiveness of Comparative Effectiveness Research*, 159 U. PA. L. REV. 2147, 2196-98 (2011) (explaining that the law of medical malpractice can interfere with the practice of evidence-based medicine). *See generally* David A. Hyman & Charles Silver, *It Was on Fire When I Lay Down on It: Why Medical Malpractice Reform Can't Fix Healthcare*, *in* OXFORD HANDBOOK OF AMERICAN HEALTH LAW (I. Glenn Cohen, Allison Hoffman & William Sage, eds., 2016).

[240] *See* Kevin R. Betts, *Physician Response to Contextualized Price-Comparison Claims in Prescription Drug Advertising*, 10 J. COMMUN. HEALTHCARE 195 (2017).

[241] *Id.* at 195.

[242] *Id.* at 196, 197.

[243] *Id.* at 195.

[244] *Id.*

[245] Pierre Azoulay, *Do Pharmaceutical Sales Respond to Scientific Evidence?*, 11 J. ECON. & MGMT. STRATEGY 551, 586 (2002) ("I find that marketing had a more pronounced direct effect on demand than science, but the latter was still statistically and economically significant.").

limitations—in addition to time constraints—can interfere with rational medical decision-making in the face of drug advertising.[246]

These dynamics may explain the fact that, even before Forest decided to undertake a "hard switch," a significant percentage of doctors moved their patients from Namenda IR to XR even though no demonstrated clinical justification for that change existed.[247] In addition, it is not clear that the physicians were aware that IR was facing a patent cliff and that, due to coverage from the newly obtained secondary patents, XR would eventually end up being significantly more expensive. Given that it is often the case that neither doctors nor patients "feel" drug price changes,[248] and that payers may not immediately appreciate them either—especially when the switch campaign is accompanied by discounts on the new drug—switches that may appear irrational from the economic perspective actually end up taking place. This "price disconnect" can, then, further contribute to unnecessary adoption of a drug having a different dosage profile or formulation followed by lock-in that results from doctors' unwillingness to "yo-yo" their patients back to the original drug version after already making one treatment change.[249] Given that, thanks to the sidestepping of generic substitution, pharma companies can make significant financial gains by inducing such treatment changes,[250] the incentive is there to put out advertising that comes as close as possible to the line of legality.

Nor were there other companies in the marketplace that could challenge the claims and thus interfere with this process. At the time the XR advertising occurred, generics were not allowed to market IR because the pioneering patent had not yet expired and, for similar reasons,[251] there were no other firms marketing alternative XR versions of Namenda. To be sure, generics could in theory market IR after the patent cliff. But as

[246] *See* Ho, *supra* note 238; *see also* Cynthia M. Ho, *Drugged Out: How Cognitive Bias Hurts Drug Innovation*, 51 SAN DIEGO L. REV. 419 (2014).
[247] As noted earlier, a later study concluded that data with respect to purportedly improved patient compliance was inconclusive at best. *See* Deardorff & Grossberg, *supra* note 223.
[248] *See* Michael A. Carrier & Steve D. Shadowen, 92 NOTRE DAME L. REV. 167, 169-70, 179-80 (2016) (calling this phenomenon a "price disconnect"); *see also* Douglas Lundin, *Moral Hazard in Physician Prescribing Behavior*, 19 J. HEALTH ECON. 639 (2000). Nonetheless, these effects might be alleviated with "consumer-driven health care" models. *See, e.g.*, Wendy Netter Epstein, *Nudging Patient Decision Making*, 92 WASH. L. REV. 1255 (2017).
[249] In addition, other marketing techniques, including "coupons" for prescribing physicians and rebate payments for insurance companies, can lead to inefficiencies in this area. *See, e.g.*, Joseph S. Ross & Aaron S. Kessleheim, *Prescription-Drug Coupons—No Such Thing as a Free Lunch*, 369 NEW ENG. J. MED. 1188 (2013).
[250] *See supra* notes _-_ and accompanying text; *see also* Emily Michiko Morris, *The Myth of Generic Pharmaceutical Competition Under the Hatch-Waxman Act*, 22 FORDHAM INTELL. PROP. MEDIA & ENT. L.J. 245, 249 (2012).
[251] *See supra* notes _-_ and accompanying text.

the *Actavis* court concluded, patients who have been switched to XR "would be very unlikely to switch back to twice-daily IR therapy even after less-expensive generic IR becomes available, due to the high transaction costs associated with Alzheimer's patients first switching from one formulation of a drug to a new formulation and then back to the original formulation."[252] This sort of result was one that Dr. Kessler was concerned with in 1993, when he noted that some switches to "controlled release ma[de] little sense" and were instead driven not by "convenience or compliance but economics"[253]—that is, brand companies' desire to charge higher drug prices thanks to follow-on patent protection.[254]

As discussed earlier, antitrust litigation confirmed that the Namenda IR to XR reformulation was pretextual, with internal documents showing that the central goal of the product change was to slow generic competition rather than seek improvements in the care for Alzheimer's.[255] Other cases demonstrate that such strategies are not unusual.[256] Given these precedents, it can be useful for physicians, patients, and payers to have some insight into brand companies' motives, as well as have a sense of what data they have generated to establish a possible clinical improvement, before contemplating a switch.[257] Nonetheless, as we have seen, sometimes the only information provided in aid of making that decision is the advertising, which may be misperceived by physicians and others. If the goal is to have a well-functioning market for small-molecule drugs and their variations, this is inadequate. As Blue Shield/Blue Cross indicated in response to the FDA's request for public comments on the issue of "Administering the Hatch-Waxman Amendments: Ensuring an Appropriate Balance Between Innovation and Access," "[t]here are anecdotal signs that

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[252] New York *ex rel.* Schneiderman v. Actavis plc, 787 F.3d 638, 647-48 (2d Cir. 2015).
[253] Kessler, *supra* note 26, at 437.
[254] *Cf.* Nicholas S. Downing et al., *Clinical Trial Evidence Supporting FDA Approval of Novel Therapeutic Agents, 2005-2012*, 311 J. AM. MED. ASS'N 368, 373-74 (2014) ("Comparative effectiveness information, which is not required as part of FDA approval and involves comparison of an intervention with an active control, was available for less than half of indications, consistent with prior research, but leaving uncertainty about the benefits and safety of these medications when compared with other available therapeutic agents.").
[255] *See supra* notes _-_ and accompanying text.
[256] *See, e.g.*, *In re* Suboxone (Buprenorphine Hydrochloride and Naloxone) Antitrust Litig., MDL No. 2445, 2017 WL 4910673, at *11 (E.D. Pa. Oct. 30, 2017); Abbott Labs. v. Teva Pharm. USA, Inc., 432 F. Supp. 2d 408, 420, 423-24 (D. Del. 2006).
[257] *See* David A. Kessler et al., *Therapeutic Class Wars: Drug Promotion in a Competitive Marketplace*, 331 NEW ENGLAND J. MED. 135 (1994); *cf.* Ernst R. Berndt & Murray L. Aitken, *Brand Loyalty, Generic Entry and Price Competition in Pharmaceuticals in the Quarter Century after the 1984 Waxman-Hatch Legislation*, 18 INTL. J. ECON. BUS. 177 (2011); Henry G. Grabowski & John M. Vernon, *Brand Loyalty, Entry, and Price Competition in Pharmaceuticals after the 1984 Drug Act*, 35 J. L. ECON. 331 (1992); Klasmeier, *supra* note 68.

reformulated products may positively impact adherence and that reformulations may improve patient outcomes, but payers need data that demonstrates improved adherence or other product benefits over existing therapies."[258]

Although data that can enable definitive comparative judgments even between closely related drug products can be difficult to generate,[259] the relevant public can still benefit from knowing for certain that no such data is available, that some data exists but is inconclusive in certain respects, or that the data shows some potential for health outcome improvements, but only for particular populations or in certain treatment settings. Given that the lack of transparency in this area could needlessly increase health care costs and perhaps even lower the quality of care, studies that develop comparative data should be encouraged and rewarded. The next section explains that, in addition to helping improve transparency in communications between pharmaceutical firms and physicians, patients, and payers,[260] mechanisms for the generation and submission of such data could facilitate longer-term improvements in medical care in the context of the program of comparative effectiveness research.

B. Comparative Effectiveness Research

As noted in the previous section, the concepts of drug safety and effectiveness cannot be pinned down with precision in an absolute sense.[261] Comparative safety and effectiveness are even more difficult to assess because comparisons can take place across a number of parameters.[262] Between two or more drugs used to treat the same condition, relative safety or effectiveness can, for example, vary depending on the sub-population of patients being treated.[263] The two drugs may have different side effects that are not readily comparable, and, even in theory, it may be difficult to make an absolute judgment as to which is "better" between drugs one of which is safer of the two and the

[258] Comment from Blue Cross Blue Shield Association (BCBSA) at 3, *Administering the Hatch-Waxman Amendments: Ensuring a Balance Between Innovation and Access*, Docket FDA-2017-N-3615 (Oct. 17, 2017), https://www.regulations.gov/document?D=FDA-2017-N-3615-0087.
[259] *See infra* notes _-_ and accompanying text.
[260] Indeed, information developed under this proposal could help sponsors legally communicate so-called "health care economic information" with payers, as contemplated by a recent amendment to the FDCA by the 21st Century Cures Act. *See* 21 U.S.C. § 352(a).
[261] *See* Lietzan, *supra* note 117; *see also supra* note 228 and accompanying text.
[262] Bloche, *supra* note 73, at 446 ("Selection of outcome measures for such [comparative studies is fraught with normative questions that lack agreed-on answers.").
[263] *See, e.g.*, Roger Chou et al., *Comparative Efficacy and Safety of Long-Acting Oral Opioids for Chronic Non-cancer Pain: A Systematic Review*, 26 J. PAIN SYMPTOM MGMT. 1026, 1028, 1042 (2003).

other, more effective.[264] Finally, how should one value improved convenience or adherence to a medication made possible, for example, by a different dosing schedule or a new drug delivery system? The sheer complexity of human health and the number of possible considerations involved makes conclusive comparisons between two different drug products difficult.[265]

All that said, even without the theoretical possibility of a decisive comparative judgment between two drug versions, relevant data that can help physicians make informed, evidence-based decisions with respect to which drug to choose in a particular scenario can still be developed.[266] For example, reduced pill burdens for patients with HIV-AIDS undergoing antiretroviral therapy have been definitively shown to decrease hospitalization and morbidity.[267] In another case, an extended-release version of a drug led to a demonstrated improvement in "activities of daily living" of Parkinson's patients over its immediate-release counterpart.[268] Finally, based on indirect comparisons between separate traditional (i.e., placebo-based) clinical trials, researchers determined that one drug for "prevent[ing] venous thromboembolism in patients after knee or hip replacement" was more effective than two others.[269] While some of these studies were based on clinical observations using already approved drugs,[270] data that can add to the storehouse of useful drug information—as the thromboembolism indirect comparison study indicates—can also be developed before approval. For extended-release drugs in particular, Dr. Kessler, the former Commissioner of Food and Drugs, explained the value of examining the correlation between "blood levels of drug over time with the clinical outcomes"[271] when a drug is converted from IR to XR, and highlighted the need for "clinical results in

[264] *Cf. supra* note 225 and accompanying text (discussing differences between efficacy and effectiveness).
[265] *See generally* Saver, *supra* note 239.
[266] *See* Cramer & Saks, *supra* note 25.
[267] *See* S. Scott Sutton et al., *Impact of Pill Burden on Adherence, Risk of Hospitalization, and Viral Suppression in Patients with HIV Infection and AIDS Receiving Antiretroviral Therapy*, 36 PHARMACOTHERAPY 385 (2016).
[268] Gilbert Block, *Comparison of Immediate-Release and Controlled Release Carbidopa/Levodopa in Parkinson's Disease*, 37 EUR. NEUROL. 23 (1997).
[269] Sebastian Schneeweiss et al., *Assessing the Comparative Effectiveness of Newly Marketed Medications: Methodological Challenges and Implications for Drug Development*, 90 CLIN. PHARM. & THERAPEUTICS 777, 786 (2011); *see also id.* (explaining that "indirect comparisons have been shown to produce valid results if applied correctly" and that "[i]ndirect comparisons can be conducted more expeditiously than de novo head-to-head randomized trials, and indirect comparisons using preapproval trials can be completed even before market authorization"). A direct comparison, in contrast, would require a "head-to-head: trial of the two drugs.
[270] For another example, see Pascal Auquier, *Comparison of Escitalopram and Citalopram Efficacy: A Meta-Analysis*, 7 INT'L J. PSYCHIATRY CLIN. PRACTICE 259 (2003).
[271] Kessler, *supra* note 26, at 440.

a variety of populations" taking XR products.[272] Such information could enable drug-makers to answer Commissioner Kessler's call to the Controlled Release Society to improve "clinical outcomes."[273]

More generally, studies such as these can contribute to the program of Comparative Effectiveness Research, or CER, which is a significant national priority. The statute that significantly broadened CER[274] and brought it into the national spotlight,[275] the American Recovery and Reinvestment Act of 2009, allocated 1.1 billion dollars toward the two initial years of CER research. A later statute, the well-known Patient Protection and Affordable Care Act (PPACA),[276] established "a permanent U.S. CER entity called the Patient-Centered Outcomes Research Institute . . . to guide the federal CER enterprise."[277] Notably, although there have been concerns that CER would mainly focus on cost-effectiveness, leading to fears of rationing of care,[278] "PPACA seems to take a pure clinical-effectiveness approach. It uses the key term 'comparative clinical effectiveness research' and describes research that looks at 'clinical effectiveness, risks, and benefits,' but nowhere does the statute mention comparing respective costs."[279] Still, information on comparative clinical effectiveness can help health care providers and patients make informed decisions with respect to whether a particular treatment is worth the cost—for example, whether evidence suggests that the more expensive, on-patent version of the drug may be worth switching to.

Research that can add to the CER program can come from many sources. As noted, evidence on comparative effectiveness may be contained in reports of clinicians' experiences, more formal studies of data on health outcomes based on the treatment path chosen, and even rigorous randomized controlled trials of the sort that the FDA requires for

[272] *Id.*
[273] *Id.* at 438, 440.
[274] Legislative efforts to install CER can be traced back to the 2003 Medicare Modernization Act, which created the first federal CER mandate. *See* ASHTON & WRAY, *supra* note 75, at xiii.
[275] Pub. L. 111-5, 123 Stat. 115, 177, 187-88 (Feb. 17, 2009); *see* 42 U.S.C. § 299b-8 (creating a Federal Coordinating Council for Comparative Effectiveness Research and providing appropriations).
[276] Pub L. 111-148, 124 Stat. 119, § 6302 (Mar. 23, 2010).
[277] Riaz Ali et al., *Comparative Effectiveness Research in the United States: A Catalyst for Innovation*, 4 AM. HEATH DRUG BENEFITS 68, 69 (2011).
[278] *See, e.g.* Scott Gottlieb, Congress Wants to Restrict Drug Access, WALL ST. J. (Jan. 20, 2009), https://www.wsj.com/articles/SB123241385775896265; *see also* Eric Sun & Tomas J. Philipson, *Blue Pill or Red Pill: The Limits of Comparative Effectiveness Research*, MANHATTAN INST. RPT. (June 28, 2011), https://www.manhattan-institute.org/html/blue-pill-or-red-pill-limits-comparative-effectiveness-research-6012.html. *But cf.* Jerry Avorn, *Debate About Funding Comparative-Effectiveness Research*, 360 N. ENGL. J. MED. 1927 (2009).
[279] Saver, *supra* note 239, at 216.

drug approval,[280] but using "comparator arms other than placebo."[281] CER does face significant challenges, including the lack of a uniform standard of comparative effectiveness[282] and the sometimes limited physician buy-in that can get in the way of implementation of information gleaned from CER at the patient treatment level.[283] In spite of the various obstacles, however, CER has led to significant successes and continues to be seen as a path forward in health care.[284] The program is continuing to gather momentum as a tool that bolsters the goals of evidence-based medicine and helps develop information that could enable health care providers cut unnecessary medical costs.[285]

In this vein, some commentators have concluded that for CER to be particularly effective, early data generation is important. This information can help ensure that therapies are not "prematurely adopted, outpacing the generation of evidence necessary to define the boundaries of where a drug or device offers clinical benefit,"[286] a situation perhaps exemplified by some physicians' switch form Namenda XR to IR. More generally, physicians can benefit from data on "whether the intervention is better than other available interventions for specific populations and whether we can identify the subgroups of patients who will benefit the most from (or are the most likely to be harmed by) specific interventions."[287] This information would seem to be particularly useful for doctors thinking of refining a treatment protocol that is already shown

[280] *See supra* notes _-_ and accompanying text.
[281] *See Federal Coordinating Council for Comparative Effectiveness Research: Report to the President and Congress* 16 (June 30, 2009), https://osp.od.nih.gov/wp-content/uploads/FCCCER-Report-to-the-President-and-Congress-2009.pdf; *see also* C. Daniel Mullins, 28 PHARMACOECON. 969 (2010); *cf.* Scott Gottlieb & Coleen Klasmeier, *Comparative Effectiveness Research: The Need for a Uniform Standard*, AEI HEALTH POL'Y OUTLOOK 4 (June 2009), http://www.aei.org/wp-content/uploads/2011/10/06%20HPO%20Gottlieb-g.pdf (suggesting the use of epidemiological and registry data in CER).
[282] *See generally* Gottlieb & Klasmeier, *supra* note 281 (suggesting "substantial clinical experience" as the uniform standard"); *see also* John K. Iglehart, *Prioritizing Comparative-Effectiveness Research—IOM Recommendations*, 321 N. ENGL. J. MED. 325 (2009).
[283] *See generally* Saver, *supra* note 239.
[284] *See, e.g.*, Kalipso Chalkidou, *Comparative Effectiveness Research and Evidence-Based Health Policy: Experience from Four Countries*, 82 MILBANK Q. 339 (2009); Louis D. Fiore & Philip W. Lavori, *Integrating Randomized Comparative Effectiveness Research with Patient Care*, 374 N. ENGL. J. MED. 2152 (2016); Robert M. Golub & Phil B. Fontanarosa, *Comparative Effectiveness Research: Relative Successes*, 307 J. AM. MED. ASS'N 1643 (2012); Laxmaiah Manchikanti et al., *The Impact of Comparative Effectiveness Research on Interventional Pain Management: Evolution from Medicare Modernization Act to Patient Protection and Affordable Care Act and the Patient-Centered Outcomes Research Institute*, 14 PAIN PHYS. E249 (2011).
[285] *See generally* ERIC M. PATASHNIK ET AL., UNHEALTHY POLITICS: THE BATTLE OVER EVIDENCE-BASED MEDICINE (2017).
[286] Alexander & Stafford, *supra* note 72, at 2488.
[287] Patrick H. Conway & Carolyn Clancy, *Comparative Effectiveness Research—Implications of the Federal Coordinating Council's Report*, 361 N. ENGL. J. MED. 328, 330 (2009).

to be safe and effective by switching to another formulation,[288] as a change in the drug form could present previously unrecognized problems.[289]

Although pre-marketing data is necessarily of more limited value than the "real-world" data actually developed after clinical practice starts, there can be an important feedback mechanism between the two. For example, pre-marketing comparative efficacy studies on ADHD drugs in Europe have yielded critical information that could be supplemented in the course of clinical practice.[290] Thus, even when not definitive, data developed by drug-makers before marketing can provide a starting point for physicians to make informed decisions and serve as an impetus for future research and data analysis.[291] In addition, a framework for rewarding data generation could foster a culture in which drug changes that are made are not pretextual or driven merely by the availability of follow-on patenting coupled with vague advertising.[292] This framework can further the FDA's mission of "advancing the public health by helping to speed innovations that make medical products more effective, safer, and more affordable and by helping the public get the accurate, science-based information they need to use medical products and foods to maintain and improve their health."[293]

Notably, though, wide-ranging adoption of CER at the FDA is not the goal of the proposal that follows.[294] The focus, instead, is strictly on follow-on products of already-approved drugs coming from the same firm.[295] This is because the product-hop pattern has demonstrated particular susceptibility to information asymmetries, market failures, and the sort of conduct that even strong supporters of incremental innovation said should be discouraged.[296] Although, as Dr. Gottlieb argued before he

[288] This assumes that the original product has not been pulled for lack of safety or effectiveness. *See* supra note 233 and accompanying text.
[289] Alexander & Stafford, *supra* note 72; O'Connor, *supra* note 72.
[290] Florence T. Bourgeois, *Premarket Safety and Efficacy Studies for ADHD Medications in Children*, 9 PLoS ONE e4102249 (2014).
[291] Alexander & Stafford, *supra* note 72.
[292] *See supra* notes _-_ and accompanying text.
[293] *See generally* U.S. FOOD AND DRUG ADMIN., *What We Do*, https://www.fda.gov/AboutFDA/WhatWeDo.
[294] *Cf.* Scott Gottlieb, *The FDA Should Not Mandate Comparative-Effectiveness Trials*, AEI HEALTH POL'Y OUTLOOK (June 2011), http://www.aei.org/wp-content/uploads/2011/10/HPO-2011-05-g.pdf (arguing against implementing CER via a requirement of proof of comparative effectiveness to obtain FDA approval).
[295] *See* Simone Ghislandi, *Product Hopping and Pre-emptive Cannibalization in Pharmaceuticals*, Working Paper, *available at* http://www.econpubblica.unibocconi.it/files/WP_169_2012.pdf (concluding that follow-on product changes take place "mainly between products of the same firm").
[296] Wertheimer & Santella, supra note 22, at 7.

became Commissioner of Food and Drugs, market factors and the draw of being able to legally advertise comparative efficacy have made mandates or other formal mechanisms to force comparative drug data generation unnecessary in many circumstances,[297] the product-hop scenario is different. Antitrust litigation has demonstrated that pretextual drug reformulations have not always been fully recognized as such by the relevant market actors.[298] In addition, particular drug changes like switches from immediate to extended release tend to have problems (impact of the "food effect" on the drug's effectiveness,[299] build-up of immunity to the effects of the drug[300]) and advantages (increased compliance[301] and safety[302]) that are recurring and somewhat predictable, limiting the number of bases of comparison relative to, for example, comparisons between two drugs having different chemical structures. Given these unique characteristic of product hops, this pattern could merit special consideration among FDA-mediated mechanisms for generating comparative data. In the meantime, the section that follows explains that such a role for the FDA would not be unprecedented, as the agency must already make comparisons between drug products in many circumstances and thus has the expertise in forming such judgments.

C. The FDA's Product-Comparison Expertise

Examples of the FDA's authority to evaluate data purporting to show differences between drug products abound.[303] For one thing, the FDA is authorized to grant so-called priority review to "applications for drugs that, if approved, would be significant improvements in the safety or effectiveness of the treatment, diagnosis, or prevention of serious

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[297] *See generally* Gottlieb, *supra* note 294.

[298] *See supra* notes _-_ and accompanying text.

[299] *See* Rabia Bushra et al., *Food-Drug Interactions*, 26 OMAN MED. J. 77, 77 (2001) ("Regarding food-drug interactions physicians and pharmacists recognize that some foods and drugs, when taken simultaneously, can alter the body's ability to utilize a particular food or drug, or cause serious side effects."); *see also* Peter A. Wintstanley & Michael Orme, *The Effects of Food on Drug Bioavailability*, 28 BR. J. CLIN. PHARMAC. 621, 621 (1989) (noting that food can interfere with drug actions based on factors other than bioavailability). *See generally* Peter G. Welling, *Effects of Food on Drug Absorption*, 16 ANN. REV. NUTR. 383 (1996).

[300] Cramer & Saks, *supra* note 25, at 485; *see also* Kessler, *supra* note 26, at 440, 441.

[301] Sutton, *supra* note 267.

[302] Kessler, *supra* note 26, at 437.

[303] Even without a general requirement of comparative efficacy, such data is available in a significant number of approval packages anyway. *See* Nikolas H. Goldberg et al., 305 J. AM. MED. ASS'N 1786, 1788 (2011) ("[A]bout half of all new drugs approved in the United States since 2000 were compared with an alternative treatment prior to market authorization, and the results of this comparison were publicly available in the FDA approval packages."). In a sense, then, this proposal formalizes what is already happening, but in a specific product setting.

conditions when compared to standard applications."[304] Second, the FDA already requires so-called "non-inferiority" trials for certain classes of drugs, such as antibiotics, which as the term suggests are designed to show that the proposed drug is no worse than what has already been approved.[305] Third, in the context of determining whether to grant regulatory exclusivity for so-called biologic drug products—which differ from small-molecule pharmaceuticals in size and method of preparation, and are subject to the Biologics Price Competition and Innovation Act (BPCIA), a regulatory regime different from the brand-generic Hatch-Waxman framework for small molecules—the FDA is authorized to consider whether a structural change "result[s] in a change in safety, purity, or potency" relative to another product marketed by the same firm.[306] This statutory section, referred to as an "anti-evergreening" provision during the legislative history of the BPCIA,[307] thus directs the FDA to consider differences between related products and prevents the same firm from "stacking" exclusivities on related products without a showing of clinical distinctiveness. As do the other two examples, this provision confirms that the FDA has already been entrusted, in some circumstances, with considering clinical differences between related drug

[304] U.S. FOOD AND DRUG ADMIN., CENTER FOR DRUG EVALUATION AND RESEARCH, *Priority Review*, https://www.fda.gov/ForPatients/Approvals/Fast/ucm405405.htm. *See generally* Erin E. Kepplinger, *FDA's Expedited Approval Mechanisms for New Drug Products*, 34 BIOTECH. L. RPT. 15 (2015). Another route for expedited approval of certain drugs that requires the FDA to make a comparative judgment is the so-called Subpart H route. *See* 21 C.F.R. § 314.500. I thank Professor Erika Lietzan for suggesting that I make this point.

[305] *See* Gottlieb, *supra* note 294, at 3-5; *see also* Zachary Brennan, *When Can Non-Inferiority Trials Establish Efficacy? FDA Explains with Guidance*, REG. AFF. PROF'LS SOC. (Nov. 7, 2016) http://www.raps.org/Regulatory-Focus/News/2016/11/07/26134/When-can-Non-Inferiority-Trials-Establish-Efficacy-FDA-Explains-With-Guidance.

[306] 42 U.S.C. § 262(k)(7)(C)(ii)(II). This statute also forbids separate exclusivity to the same firm for "a change (not including a modification to the structure of the biological product) that results in a new indication, route of administration, dosing schedule, dosage form, delivery system, delivery device, or strength." *Id.* § 262(k)(7)(C)(ii)(I); *see also* James E. Valentine & James C. Shehan, *FDA's New Biosimilars Guidance Has Sponsors Provide Information to Win Reference Product Exclusivity; Liberal Criteria Opens the Door to More Exclusivities Being Awarded*, FDA LAW BLOG (Aug. 9, 2014), www.fdalawblog.net/fda_law_blog_hyman_phelps/2014/08/fdas-new-biosimilars-guidance-has-sponsors-provide-information-to-win-reference-product-exclusivity-.html (discussing "meaningful benefit to public health, such as a therapeutic advantage" aspect of the FDA guidance expounding on this statutory section).

[307] Kurt S. Karst, *BPCIA's Principal Authors Seek to Clarify Congressional Intent with Respect to 12 Year Exclusivity Period; PhRma/BIO Request "Umbrella Exclusivity"*, FDA LAW BLOG (Jan. 5, 2011), http://www.fdalawblog.net/2011/01/bpcias-principal-authors-seek-to-clarify-congressional-intent-with-respect-to-12-year-exclusivity-pe ("[Public Health Service] Act § 351(k)(7)(C) is intended to prevent evergreening by excluding most product changes from qualifying for a new 12-year exclusivity period."); *see also* Janet Freilich, *Patent Infringement in the Context of Follow-on Biologics*, 16 STAN. TECH. L. REV. 9, 23 (2012) ("[T]he BPCIA includes an "anti-evergreening" provision: a list of improvements in a drug that do not qualify for an exclusivity period--an effort to reduce the strategic small improvements made by producers of small molecule drugs in an attempt to extend their market monopoly.").

products during the approval process. More significantly for the purposes of this Article, this section differentiates product changes by a firm that marketed the original product from improvements made by third parties.

Finally, in the context of small-molecule drugs, the FDA is authorized to grant a three-year regulatory (i.e., non-patent) exclusivity period for "reports of new clinical investigations . . . essential to the approval of"[308] modifications of already approved drug products that "affect its active ingredient(s), strength, dosage form, route of administration or conditions of use."[309] Although no comparative analysis is required, this determination requires generation and evaluation of data that could at least provide a starting point for comparisons between two forms of the drug. Interestingly, Congress has recently considered adopting the standard of "significant clinical benefit in comparison with existing therapies" for granting this type of exclusivity,[310] in line with a similar approach of the European Medicines Agency, the FDA's European equivalent.[311] But even if this approach becomes law,[312] the fact remains that the three-year period is often dwarfed by patent-based exclusivities for follow-on formulations, effectively rendering this provision superfluous if a brand company obtains a follow-on patent with significant term past the expiration of the pioneering one.

Although the proposal that follows does not impose a heightened European-style standard for the approval of follow-on drugs, it does suggest that the FDA should formally acknowledge the reality of product hopping and seek to reward firms that make good-faith attempts to develop comparative data between drug formulations relative to those that do not. In doing so, the FDA would be able to harness its well-

[308] 21 U.S.C. § 355(c)(3)(E)(iii).

[309] *See* U.S. FOOD AND DRUG ADMIN., *Small Business Assistance: Frequently Asked Questions for New Drug Product Exclusivity*, https://www.fda.gov/Drugs/DevelopmentApprovalProcess/SmallBusinessAssistance/ucm069962.htm.

[310] Kurt S. Karst, *The Improving Access to Affordable Prescription Drugs Act: A Different Tack on Exclusivity*, FDA LAW BLOG (Apr. 5, 2017), http://www.fdalawblog.net/fda_law_blog_hyman_phelps/2017/04/the-improving-access-to-affordable-prescription-drugs-act-a-different-tack-on-exclusivity.html (discussing a proposed bill that would adopt such language for additional exclusivity based on new clinical investigations).

[311] See GUIDE TO EU PHARMACEUTICAL REGULATORY LAW 241 (Sally Shorthouse ed. 2011).

[312] *Cf. generally* John R. Thomas, *The End of "Patent Medicines"? Thoughts on the Rise of Regulatory Exclusivities,* 70 FOOD & DRUG L.J. 39 (2015) (contending that the FDA exclusivities have come to play a bigger role than patent protection in incentivizing pharmaceutical innovation); *see also* Amanda Fachler, *The Need for Reform in Pharmaceutical Protection: The Inapplicability of the Patent System to the Pharmaceutical Industry and the Recommendation of A Shift Towards Regulatory Exclusivities*, 24 FORDHAM INTELL. PROP. MEDIA & ENT. L.J. 1059, 1070 (2014).

established function as an information intermediary, helping the market distinguish product-hop "lemons" from product changes that may embody genuine innovations.[313] In performing this task, the FDA can fill the gaps left open by the patent system, which is not well-equipped to deal with these questions. Moreover, the FDA's invigorated role may take the pressure off courts deciding antitrust cases predicated on product-hopping theories,[314] whose institutional capacity to evaluate technical data may be limited and that are, in any event, acting after the alleged harms have occurred, rather than preventively. If the problem is one of regulatory design in a highly regulated industry, the solution that invites itself is to fix the design, rather than deal with it ex post with antitrust actions.[315] That solution follows.

IV. INDUCING SUBMISSION OF DRUG-COMPARISON DATA TO THE FDA

A. The Threshold Standard and the FDA's Task

A number of mechanisms for inducing the submission of data relevant to drug comparisons are conceivable. But the threshold issue is the standard that the sponsor must meet to obtain benefits designated for companies who have differentiated themselves from those that submitted no relevant information. Given that the concept of comparative efficacy is quite indeterminate, the standard is best left open-ended—for example, framed as "data relevant to relative performance of new product versions." The goal is for the FDA to identify, and put the public on clear notice of, product changes for which the sponsor provided no comparative data at all, or no credible data indicative of any colorable difference between the products. Although the standard is not meant to be a demanding one, its adoption can, nonetheless, induce the generation of information of value to the public. Significantly, as further explained below,[316] because the proposed framework focuses principally on regulation of conduct rather than speech, it largely sidesteps First

[313] *See generally* Katz, *supra* note 66.

[314] *See* Carlton, *supra* note 61, at 503 (explaining that "the regulatory solution should be to fix Hatch-Waxman, rather than misuse antitrust law to impose an obligation on firms to assist rivals' efforts to free-ride"); Devin & Jacobs, *supra* note 59; *see also* Matthew G. Sipe, *Patent Privateers and Antitrust Fears*, 22 MICH. TELECOMM. & TECH. L. REV. 191, 195-96 (2016) (explaining that antitrust law should be a measure of last resort when regulatory alternatives are available). *See generally* Matthew G. Sipe, *Patents and Antitrust: Preempting Conflict*, 66 AM. U. L. REV. 415 (2017) (discussing the Supreme Court's tendency to conclude that antitrust actions are preempted by other regulatory schemes).

[315] Cynthia M. Ho, *Should All Drugs Be Patentable? A Comparative Perspective*, 17 VAND. J. ENT. & TECH. L. 295, 320 (2015) (explaining that "[a]lthough . . . actions [like those by Forest] properly prompt antitrust disputes, the need for such actions may still result in a delay in generic competition").

[316] *See infra* notes _-_ and accompanying text.

Amendment problems that the FDA faces when it seeks to limit promotion of off-label prescribing and the like.

Although the FDA would apply the proposed standard on a case-by-case basis, studies that could qualify under the relevancy standard could be satisfied by at least the following types of submissions: (1) for extended-release products and new dosage forms, studies examining patient compliance, the presence or absence of the food effect on the drug's effectiveness, and so on; (2) for certain products that embody "purer" versions of previously approved drugs, to be further discussed below,[317] studies designed to determine whether a reduction in a signature side effect associated with the original version of the drug has been observed; (3) indirect comparisons via analysis of clinical trial data gathered separately for the original and modified products; (4) studies showing that the new drug version meets the "change in safety, purity, or potency" standard used to compare biologic products; (5) non-inferiority data of the sort required for antibiotics and other anti-infective drugs; (6) formal, randomized head-to-head clinical trials designed to assess relative safety and effectiveness of the two drug forms; (7) any other information FDA deems relevant to the question of drug comparison, such as data on relative effectiveness of the two versions in particular sub-populations. Of course, some of the suggested options for comparing drug products would be more expensive for the sponsor than others. On the plus side for companies that do more, though, truthful advertising claiming that a drug change represents a definitive improvement—with the stamp of FDA approval—would then be legally possible.[318] And of course, given that a proven improvement in a drug formulation is a pro-competitive justification and embodies a non-pretextual change, that stamp of approval should preclude antitrust liability even in a case of a "hard switch."[319]

The FDA could invite sponsors to submit comparison evidence as it examines data proffered for regular NDA approval of the modified product.[320] The sponsor, incidentally, could sometimes rely on the evidence used for meeting the basic statutory standard of "safe and effective" over a placebo for the old and new versions in order to also prove up a comparison.[321] For example, if the sponsor seeks to establish a difference between two drug versions via an indirect comparison or a

[317] *See infra* notes _-_ and accompanying text.
[318] *See infra* notes _-_ and accompanying text.
[319] *See supra* notes _-_ and accompanying text. *Cf.* Stacey L. Dogan & Mark A. Lemley, *Antitrust Law and Regulatory Gaming*, 87 TEX. L. REV. 685 (2009).
[320] In certain circumstances, the application could take a form of the so-called supplemental NDA.
[321] *See* 21 U.S.C. § 355(b); *id.* § 393(b)(2)(B).

non-inferiority study, the regular safety and effectiveness data could be used as baselines.[322] Whatever method the sponsor relies on, the FDA's task would be to determine whether the proffered information has scientific relevance to the question of comparative drug efficacy. "Studies" of the sort introduced in the Namenda secondary patent prosecution, for example, would be rejected under this standard.[323] If doubts with respect to the data's relevancy remain, FDA officials could request that the sponsor submit a clarifying explanation or, perhaps, further data. As with other FDA decisions, third parties could weigh in by submitting so-called citizen petitions aiming, for example, to persuade the agency that the sponsor's evidence falls short.[324]

In the process of examining the submissions, FDA officials would naturally develop insight into the question whether, and in what dimension, the improvement provides a provably different clinical option from the original. The agency would then summarize its conclusions and require that information to be added to the drug label.[325] If the FDA concludes that no relevant data was submitted, then it would mandate that the sponsor indicate this fact on the label in a prominent way. The section that follows discusses in greater detail both potential market and regulatory rewards for sponsors who provide data that passes the relevancy threshold.

B. Incentive Mechanisms

The next, critical, aspect of the proposal concerns rewards for sponsor firms that produce adequate comparative data relative to those that do not. Perhaps, the label notation in which the FDA summarized the comparative data, if any, that the sponsor had submitted can be a sufficient reward in itself. Payers may decline to cover a more expensive, newly patented drug version based on their read of the information in the label, and benefit managers may exclude such drugs from formularies.[326] Although physicians' perception of the matter on the label would still be subject to schemas and other cognitive limitations,[327] information that is clearly communicated and included with the drug at the behest of the

[322] *See supra* notes _-_ and accompanying text.
[323] *See supra* notes _-_ and accompanying text.
[324] *See* 21 C.F.R. § 10.30.
[325] *Cf.* Evans, *supra* note 225, at 504 (discussing the role of labels and the challenges of relying on them).
[326] Comment from Blue Cross Blue Shield Association (BCBSA) at 3, *Administering the Hatch-Waxman Amendments: Ensuring a Balance Between Innovation and Access*, *supra* note 258; *see also* Henry Grabowski & C. Daniel Mullins, *Pharmacy Benefit Management, Cost-Effectiveness Analysis and Drug Formulary Decisions*, 45 SOC. SCI. MED. 535 (1997).
[327] *See supra* notes _-_ and accompanying text.

FDA may be more helpful for making rational decisions than claims in pharmaceutical company advertisements. Thus, even in the face of the advertisements, physicians could become wary about prescribing the reformulated drug where no relevant comparative data was proffered and described on the label, or where the data does not tend to show that patients would benefit from the change.[328]

These decisions could ultimately reward those sponsors who have made a credible case that the new version provides an advantage in some respect over the original or, at the very least, has been shown to be unlikely to lead to complications that can be associated with the switch. Conversely, sponsors who have failed to submit relevant comparative data may fare less well in the now better-informed market for pharmaceutical drugs, particularly when the new version is significantly more expensive due to patent protection. To be sure, physicians would be free to prescribe the modified version of the drug in any event. For example, they could choose to opt for it if post-approval evidence of the follow-on drug's utility develops based on clinical experience or more formal studies, a hunch that the follow-on version would work better for a particular patient—for example, an extremely forgetful individual for whom a lower pill burden would be critical no matter what the cost—or perhaps even as a "shot-in-the-dark" alternative if the pioneering drug just does not seem to be working. The goal is not to keep the modified drug off the market,[329] but rather to put the relevant public on clear notice of what, if any, comparative drug analysis the sponsor conducted prior to approval and what that analysis might lead one to conclude.

The role of patents and their influence on relative drug prices are worth examining further. As discussed earlier, the promise of exclusivity from secondary patents may often drive brand companies to develop, obtain approval for, and market drug reformulations.[330] Although the proposal applies to certain drug modifications without regard to whether secondary patents that cover them exist, its most significant impact would be on follow-on drugs that are patented because pretextual product changes most often occur when the patent cliff approaches, triggering a

[328] *But cf.* Elissa Philip Gentry, *Relinquishment of Inappropriate Off-Label Uses: The Effect of the False Claims Act*, https://ssrn.com/abstracts=2911372 (discussing evidence that physicians do not always examine drug labels carefully).

[329] *See* RICHARD A. EPSTEIN, OVERDOSE 57 (2006); *see also* Richard A. Epstein, *Some Criticisms of the Pharmaceutical Industry Critically Re-examined*, *in* INNOVATION AND THE PHARMACEUTICAL INDUSTRY 100, 122 (H. Tristram Engelhardt, Jr. & Jeremy R. Garrett eds., 2008); *see also* Ross D. Petty, *Limiting Product Choice: Innovation, Market Evolution, and Antitrust*, 21 J. PUB. POL'Y MARKETING 269 (2002).

[330] *See supra* notes _-_ and accompanying text.

"prevention" strategy enabled by the new patents.[331] Comparative information, then, can help market participants identify potentially sham innovations with the aid of the FDA and decide for themselves whether the newly patented formulations are worth the cost. But a further approach to differentiate between firms that submit the information and those that do not could include more aggressive regulatory measures that would have the effect of driving down prices of follow-on products for which no relative comparative data exists. One potential approach concerns the privilege of having a patent covering a drug product listed in the Orange Book.

As discussed in Part I, the Orange Book provides an important linking mechanism between pharmaceutical patents and FDA approval.[332] To obtain an Orange Book listing, brand companies "shall file with the [NDA] the patent number and the expiration date of any patent which claims the drug for which the applicant submitted the application . . . and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use, or sale of the drug."[333] To recap, the Patent Act deems the filing of an ANDA to market a generic version of a branded drug covered by one or more unexpired Orange Book-listed patents an act of patent infringement.[334] To seek approval of an ANDA when such patents exist, the generic firm must file a so-called Paragraph IV certification with the FDA, setting forth the basis as to why each patent is invalid or not infringed.[335] Once the brand initiates the patent suit typically triggered by such a filing, FDA approval of the ANDA is postponed for at least 30 months unless all of the asserted Orange Book patents are adjudged to be invalid or not infringed before that time.[336]

The certification requirement and the 30-month delay are significant regulatory benefits for brand companies who obtain approvals for their NDAs, and they are available for both pioneering and follow-on drugs.[337] To create a stronger form of inducement for comparative data generation, the FDA could be authorized to exclude patents of sponsors

[331] *See supra* notes _-_ and accompanying text. Of course, that information would also be useful for decisions with respect to products made more expensive due to the three-year regulatory exclusivity as opposed to a patent exclusivity.
[332] *See supra* notes _-_ and accompanying text.
[333] 21 U.S.C. § 355(b)(1).
[334] 35 U.S.C. § 271(e)(2).
[335] 21 U S C. § 355(j)(2)(A)(vii)(IV).
[336] *Id.* § 355(j)(5)(B)(iii).
[337] *See generally* Bouchard et al., *supra* note 92.

who fail to meet the relevancy threshold from the Orange Book.[338] Without the listings, brand companies can still sue generics for patent infringement once the latter launch the products under their ANDAs, and thus face the risks of retrospective damages and potentially an injunction against further marketing of the generic product.[339] Nonetheless, at least approvals will not be delayed by Paragraph IV certifications and 30-month stays, and given how frequently courts invalidate follow-on patents, the risks may be worthwhile for the generics to take.[340] In addition, even if found liable, generic companies may convince courts that an injunction is unwarranted because the equities, and particularly the public interest factor, favor them[341]—or that damages (if determined under the reasonable royalty measure) should be low because a hypothetical license as a stand-in for the reasonable royalty measure of damages would not have a very high value in these circumstances.[342]

A fair question to ask at this point is whether generics would even wish to enter once the FDA has concluded that no provable difference between the old and new versions exists. As noted above, though, doctors may still decide to prescribe the reformulated drug for various reasons,

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[338] *Cf.* Jacob S. Sherkow, *Administrating Patent Litigation*, 90 WASH. L. REV. 205, 214-15, 250-253 (2015) (calling for greater role for the FDA to police Orange Book listings); *see also* Eisenberg & Crane, *supra* note 61. There is, incidentally, already some existing "discrimination" between patents at the patent-FDA regulatory interface. For example, only one Orange Book patent covering a drug is eligible for term extension to account FDA delays under 35 U.S.C. § 156(c)(4), and patents eligible for extension are limited to "pioneering" forms of drugs, *id.* § 156(a)(5). *See* Lisa Larrimore Ouellette, *How Many Patents Does It Take to Make a Drug?—Follow-On Pharmaceutical Patents and University Licensing*, 17 MICH. TELECOMM. & TECH. L. REV. 299, 306 (2010) ("Only one patent per drug may be extended, and extensions are granted only for 'the first permitted commercial marketing or use of the product,' meaning that a patent owner cannot extend a patent on a drug that is merely a new formulation of an old 'product.'" (citing 35 U.S.C. § 156(a)(5)). Nonetheless, patent extensions under this sections have been allowed for so-called "prodrugs." *See* Photocure ASA v. Kappos, 603 F.3d 1372 (Fed. Cir. 2010); *see also infra* notes _-_ and accompanying text (discussing prodrugs); *cf.* Ouellette, *supra*, at 312 & n.84 (discussing this result).

[339] *See* 35 U.S.C. § 271(a)-(c); *see* AstraZeneca AB v. Apotex Corp., 782 F.3d 1324, 1330-32 (Fed. Cir. 2015).

[340] *See* Hemphill & Sampat, *supra* note 45. I thank Jonathan Darrow and Gregory Dolin for discussions that led to the development of this aspect of this Article's proposal.

[341] *See, e.g.*, Johnson & Jonson Vision Care, Inc. v. CIBA Vision Corp., 712 F. Supp. 2d 1285, 1290 (M.D. Fla. 2010). Because of de-linking from the Orange Book, the patentee will not have a remedy of an automatic injunction under 35 U.S.C. § 271(e)(4)(B), another important benefit of the listing. *Cf.* Schering Corp. v. Geneva Pharm., Inc., 275 F. Supp. 2d 534, 536-37 (D.N.J. 2002), *aff'd*, 339 F.3d 1373 (Fed. Cir. 2003).

[342] *Cf. AstraZeneca*, 782 F.3d at 1344 (discussing the role of the "value of what was taken" in the reasonable royalty analysis). If the lost profits measure is chosen instead, the amount of the award might be limited by the fact brand sales are subject to generic substitution laws. *See* David Manspeizer, *The Law on Damages in Generic Drug Launches Remains Vague* 2, N.Y. L.J. (Jan. 6, 2014), https://www.wilmerhale.com/uploadedFiles/WilmerHale_Shared_Content/Files/PDFs/NYLJ-IP-the-law-on-damages-in-generic-drug-manspeizer-1-6-14.pdf.

and a price reduction thanks to the generic entry unimpeded by the Orange Book, as well as state substitution laws, would make that decision more palatable for payers.[343] Indeed, a relatively cheap, even if unproven, alternative drug option may be well-received by the market. Although brand companies might balk at the prospect of effectively supplying society with cheap drug alternatives, good-faith generation of data would help them avoid this result. Thus, the proposed framework would discourage pretextual changes, provide a market signal as to whether a more expensive drug version is worth the price, and generate data that would be useful for physicians' initial prescribing decisions and as a starting point for downstream CER. Indeed, in "motivating the provision of information"[344] in the drug-comparison scenario, the FDA could also help drive medical and scientific innovation.

Other data-inducing mechanisms may be possible, but they are likely to encounter serious legal challenges. For example, the FDA could demand that the brand disclaim enforcement of secondary patents if it seeks to market a follow-on product without providing relative comparison data. Nonetheless, this approach could be challenged as imposing unconstitutional conditions by forcing patentees to give up a part of their property right in exchange for a favorable regulatory action,[345] constituting—relatedly—a compensable taking within the meaning of the Fifth Amendment,[346] or even violating the provision of the Agreement of Trade-Related Aspect of Intellectual Property Rights that prohibits "discrimination" against patents in a particular technology field.[347]

The FDA could also change its "therapeutic equivalence" standards so that different drug forms like immediate and extended release can be interchanged under state generic substitution laws.[348] But this move might be viewed as undermining prescribers' autonomy and enabling states to, in effect, interfere with the practice of medicine[349]

[343] *See supra* notes _-_ and accompanying text.
[344] Eisenberg, *supra* note 74, at 349, 373.
[345] *See* Koontz v. St. Johns River Water Mgmt. District, 133 S. Ct. 2586, 2594-97 (2013).
[346] *See, e.g.*, Ruckelshaus v. Monsanto Co. 467 U.S. 986 (1984).
[347] TRIPs Agreement, Art. 27.1. For a recent analysis of this issue in a different context, see Daniel Harris Brean, *Business Methods, Technology, and Discrimination*, 2018 MICH. ST. L. REV. (forthcoming), https://ssrn.com/abstracts=3071000. For a suggestion that a restriction of patent rights in the context in which other forms of exclusivity are available might survive such a challenge, see Heled, *supra* note 50, at 469; *see also* Eisenberg, *supra* note 74, at 365-66; *cf.* Daniel J. Gervais, *Patents Are Optional* (on file with author).
[348] *Cf. supra* notes _-_ and accompanying text.
[349] *See* 21 U.S.C. § 396 (stating that the FDA has no authority to regulate the practice of medicine, including prescribing decisions).

through federal regulation.[350] If a physician has a hunch that a specific version of the drug that has otherwise been approved by the FDA should be prescribed given the information that is available—recall the forgetful patient for whom a smaller number of pills provides a decisive clinical advantage—then government actors should respect that decision, just as they respect decisions to prescribe off-label.[351]

Finally, instead of asking for comparative data before approval, the FDA could require brand firms to undertake post-approval investigations modeled on so-called Phase IV studies.[352] The FDA sometimes commissions these studies in order to monitor a drug's safety after marketing begins,[353] but the agency's Phase IV authority can lead to development of other kinds of information. By regulation, the sponsors could be asked to provide information with respect to "the drug's risks, benefits, and optimal use," and which may "include, but would not be limited to, studying different doses or schedules of administration than were used in phase 2 studies"—a part of the regular approval process—as well as "use of the drug in other patient populations or other stages of the disease."[354] Given that comparative data developed in the course of clinical practice is often more useful than that created under the relatively artificial pre-approval conditions,[355] this alternative approach carries potential promise. Nonetheless, there is particular value in putting physicians on notice of what the sponsor has done at the time the reformulated drug goes on the market. For one thing, that information can act as a market signal that the drug change might actually produce patient benefits, and it also serves as a check on company advertisements intended to convince prescribers to switch. Given the transaction costs of switching back, supplying physicians with some comparative data at the

[350] *See generally* Patricia J. Zettler, *Toward Coherent Federal Oversight of Medicine*, 52 SAN DIEGO L. REV. 427 (2015); *see also* Lars Noah, *State Affronts to Federal Primacy in the Licensure of Pharmaceutical Products*, 2016 MICH. ST. L. REV. 1; *cf.* Lewis A. Grossman, *Drugs, Biologics, and Devices: FDA Regulation, Intellectual Property, and Medical Products in the American Healthcare System*, *in* OXFORD HANDBOOK OF AMERICAN HEALTH LAW (I. Glenn Cohen, Allison Hoffman & William Sage, eds., 2016).

[351] *See supra* notes _-_ and accompanying text.

[352] *See* 21 C.F.R. § 312.85 (2010) (setting forth the FDA's authority to require Phase IV studies).

[353] U.S. FOOD AND DRUG ADMIN., CENTER FOR DRUG EVALUATION AND RESEARCH, *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act*, https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM172001.pdf

[354] *Id. But cf. Comparative Clinical Effectiveness and Cost-Effectiveness Research*, *supra* note 225, at 4 ("Although conducted after FDA approval, post-marketing (also known as phase IV) studies are not necessarily effectiveness studies, and only rarely could be classified as comparative effectiveness studies.").

[355] *See id.* at 4-5.

time the new product goes on the market could be integral for informed decision-making.[356] But to be sure, a requirement for post-approval CER by brands and this Article's proposal of pre-marketing comparative analysis are not mutually exclusive.

C. Implementation Mechanics

1. Specifying the Statutory Change

The next set of issues to consider concerns the FDA's authority to implement the proposal and the parameters for delimiting this authority. The requirement of a clear statement with respect to the existence of comparative data on the product label, as well as a summary of what the data teaches, is a new one for the FDA to impose. Non-inferiority studies for antibiotics,[357] for example, are a condition of approval of those drugs under the general, extant "safe and effective" standard.[358] Under this proposal, however, comparative studies are intended instead to supply the FDA and the market with some information about an already approvable drug. In addition, the "relevancy of the data for making a comparison standard" advanced here is different from the general standard. Accordingly, if the FDA is to mandate placing a summation of comparative data, or a statement that no relevant data exists, on the label, an amendment to the FDCA is necessary.

One critical task for the FDA under the proposed amendment would be to identify categories of drug changes that would be subject to the "product-hop" regime. While this legislative task is challenging, it is made simpler by the template contained in the FDA's own, already existing procedures for classifying NDAs by product type. The different NDA product categories that the FDA recognizes include the "New Molecular Entity" category (Type 1), which covers drugs having "an active ingredient that contains no active moiety that has been previously approved by the FDA"; "New Active Ingredient" drugs, which involve relatively routine chemical modifications of already-approved molecular entities with the active moiety unchanged, such as formation of so-called "esters" or "salts" (Type 2); "New Dosage Forms," a category that may include drugs having a composition identical to that of an already approved drug product (Type 3); "New Combination," chemical or physical, of two separate drugs—a category that, as relevant here, includes two drugs both of which have already been approved (Type 4); and "New Formulation," a category that, as relevant here, includes

[356] *Cf. supra* notes _-_ and accompanying text.
[357] *Cf. supra* notes _-_ and accompanying text.
[358] *See* 21 U.S.C. § 355(b).

"changes in inactive ingredients that require . . . clinical studies for approval," a product that "contains an active ingredient or active moiety that has been previously approved or marketed in the United States only as part of a combination," or a product that "contains a different strength of one or more active ingredients in a previously approved or marketed combination" (Type 5).[359] Therefore, in spite of relying on the "safe and effective" standard for all new approvals and carefully noting "[t]hese codes are not indicative of the extent of innovation or therapeutic value that a particular drug represents,"[360] the FDA already recognizes the reality that there are different kinds of drug inventions. While one of these categories, Type 1, calls out a completely new chemical ingredient, the rest of the recited categories are not and therefore provide an excellent starting point for an inclusive "product modification" class that would be subject to the proposed legislative regime.

In addition to these categories, experience has taught that there are other recurring patterns of drug changes that may be associated with exclusivity extensions based on pretextual reasons. One contentious area includes a product change from so-called "racemate" drugs to pure "enantiomers," which—to simplify the chemistry significantly—entails the marketing of a purer form of an already known drug.[361] The issue with racemates is that, given the peculiarities of chemical synthesis, they include a 50-50 mixture of two products where the first is typically the active ingredient that acts on the biological target to treat the indicated condition, while the second is essentially an impurity that is either inactive, or is, worse, sometimes a pernicious component of the drug product that has undesirable side effects.[362] Accordingly, racemate separation to isolate the "good" enantiomer for use as a new drug product is an established strategy in the drug development process. While a well-known company, Sepracor, specializes in separating the enantiomers from racemates of other companies' drugs and obtaining approval for the new products,[363] more often than not—as with many drug modifications—a company that markets the racemate also markets the pure, "better" enantiomer, generating the product-hopping concerns that

[359] U.S. FOOD AND DRUG ADMIN., *FDA Manual of Policies and Procedures*, NDA Classification Codes, https://www.fda.gov/downloads/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cder/manualofpoliciesprocedures/ucm470773.pdf.
[360] *Id.* Conceptually similar to these categories might be enantiomers, metabolites, and prodrugs, discussed below.
[361] *See generally* Darrow, *supra* note 157.
[362] *Id.* at *9.
[363] *Id.* at *13.

are present in the switch from immediate- to extended-release drug versions.[364]

Although the patenting of enantiomers sometimes runs into obviousness problems at the PTO or the courts, these determinations are of course made on a case-by-case basis and many enantiomer patents do make it past the PTO.[365] Sometimes, to bolster patentability, the patentee makes the claim that the pure enantiomer provides significant clinical benefits for patients over the racemate.[366] Nonetheless, as discussed above, these sorts of claims are best evaluated by the FDA rather than the PTO[367]—or, at the very least, the FDA may wish to conduct its own analysis of the matter in the context of a comparative evaluation. In addition, the putative benefit of switching from a racemic form of a drug to a pure enantiomer is generally somewhat predictable—often, the benefit includes reduced side effects due to the absence of the "bad" enantiomer—so studies providing data of relevance for comparison between the racemate and enantiomer version of the drug can be readily designed. Without this data, reasonable suspicion that the change could have been a pretextual one, driven solely by the availability of a patent for the purpose of attempted extension of exclusivity, could be fairly raised. In sum, because the racemate-enantiomer pattern closely resembles the paradigmatic extended-release/immediate-release pattern discussed throughout the Article, enantiomer marketing by the same firm that marketed the racemate should be subject to the proposed regime.

An interesting example of a drug modification that may not involve a clinical benefit, but nonetheless could be a bona fide upgrade, is a change that improves the drug manufacturing process, makes it easier to store the drug by, for example, producing a new crystalline form, and so on.[368] For these sorts of reformulations, perhaps a separate "manufacturing improvement" category could be created, so that rather than submitting data tending to indicate a potential difference in clinical benefit between two drug versions, the sponsor would introduce evidence tending to show improvements in handling. Here, though, the requirement of putting the information on the label would do little good, since doctors and payers are likely to care little about changes of this sort in the clinical context—unless, of course, the product is purer or

[364] *Cf. supra* notes _-_ and accompanying text.
[365] *See generally* Lemley, *supra* note 161.
[366] *Id.* at 1376-79. Sometimes, though, patentability is bolstered by the technical difficulty of separating enantiomers. *Id.* at 1384-85.
[367] *See supra* notes _-_ and accompanying text.
[368] *See generally* W. Nicholson Price II, *Making Do in Making Drugs: Innovation Policy and Pharmaceutical Manufacturing*, 55 B.C. L. REV. 491 (2014).

somehow better for patients in other ways. Nonetheless, patents on methods of manufacture are not listable in the Orange Book,[369] which perhaps limits the appeal of a product-hop strategy using this method.

Thus, the proposed framework may not function as a proper regulatory remedy for dealing with product hops involving manufacturing changes. And if the FDA becomes suspicious that anticompetitive conduct is nonetheless afoot in these circumstances, it could refer the case to the FTC for an inquiry into a potential antitrust violation. Although the antitrust route remains available for other suspected sham modifications as well, it should generally be viewed as an option of last resort given the uneasy fit of antitrust law in this area.[370] If the FDA can remedy the problem via tiered regulatory incentive structures to reward good-faith improvers, it should do so rather than leave the fix entirely to antitrust law—unless a special case, such as one involving a sham manufacturing change supported by method of manufacture patent claims, presents itself. In contrast, for patents that actually cover the drug product and are therefore eligible for an Orange Book listing, including patents on a new and allegedly more easily stored crystalline form of a drug, exclusion from the Orange Book in the absence of comparative handling data may be a reasonable option.[371]

One category of inventions that should be exempted from the ambit of the proposal, however, are newly discovered methods of use of known compounds.[372] First, these inventions do not really involve a product change as such, and therefore do not fit into a product-hopping model. Second, allegations of "sham" new indications are not often made and would indeed be somewhat incoherent, because FDA approval is required to market a drug for a new indication. Third, if anything, new methods of use of known compounds are typically difficult to protect by patents because merely manufacturing the drug without encouraging the patented use is not an act of infringement[373]—and brand companies

[369] 21 U.S.C. § 355(b)(1); *see also* 21 C.F.R. § 314.53(b).

[370] *See supra* notes _-_ and accompanying text. If no comparative effectiveness is shown, though, antitrust law remains as a weapon against certain product hops, particularly in cases of hard switches.

[371] *Cf. supra* notes _-_ and accompanying text.

[372] Likewise, the proposal does not apply to modifications of products that have never been approved or marketed as drugs. In this way, the proposal differs from (for example) India's approach, which holds that a modification of any known chemical compound for which an improvement in efficacy is not shown is obvious as a matter of that country's patent law. *See* Jodie Liu, *Compulsory Licensing and Anti-Evergreening: Interpreting the TRIPS Flexibilities in Sections 84 and 3(d) of the Indian Patents Act*, 56 HARV. INT'L L.J. 207 (2015).

[373] *See* Warner-Lambert Co. v. Apotex Corp., 316 F.3d 1348 (Fed. Cir. 2003); *see* Rebecca S. Eisenberg, *The Problem of New Uses*, 5 YALE J. HEALTH POL'Y L. & ETHICS 717, 718 (2005); Benjamin N. Roin, *Solving the Problem of New Uses* (Oct. 2016) (unpublished manuscript),

typically do not sue physicians who decide to prescribe the drug for the new indication for practical reasons. Finally, so-called "repurposing" or discovery of new indications of known chemicals has frequently led to highly significant health advances.[374] Perhaps, in the frame of this Article, discovery of a new indication is a "per se" clinical advance that easily satisfies the relevancy standard—though for ease of administration it should be excluded from the ambit of the proposal altogether.

2. A Limited Initial Adoption?

Because the new authority could represent a significant change for the FDA, alternative approaches for test-driving the proposal before making a full-on, permanent statutory change are worth exploring. For one thing, the FDA could start off by instituting a pilot program for inviting voluntary submission of comparative data by companies who would like to market the reformulated product with a label notation indicating potential advantages over the original. Voluntary programs at the FDA are numerous, and include such diverse initiatives as post-approval safety monitoring of medical devices[375] as well as a food safety regulatory program.[376] Under this approach, the drug marketed by sponsors who submit no relevant comparative data would be silent on this point, rather than affirmatively indicating the absence of it. Those who opt in, though, can get the market benefit of claiming an FDA-acknowledged difference between original and follow-on products, as well as immunity from antitrust liability.[377]

Another option for test-driving this proposal is its adoption for a very limited scope of product modifications. For example, the FDA's comparative-evaluation authority could initially cover only changes that are particularly likely to embody prevention strategies, like new formulations or dosage forms, and Congress could then consider expanding the scope of that authority if the "pilot" statute is successful.

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available at https://www.bu.edu/law/files/2016/10/Solving-the-Problem-of-New-Uses-Ben-n.-Roin.pdf. *But cf.* Sam Halabi, *The Drug Repurposing Ecosystem*, 20 YALE J. L. & TECH. 1 (2018), (contending that new pharmaceutical uses of known chemical compounds are often found without traditional exclusivity incentives).

[374] *See, e.g.*, Burroughs Wellcome Co. v. Barr Labs., Inc., 40 F.3d 1223 (Fed. Cir. 1994) (upholding the validity of a method of use patent for treating the symptoms of HIV-AIDS).

[375] U.S. FOOD AND DRUG ADMIN., *Voluntary Compliance Improvement Program (VCIP) Pilot*, https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/MedicalDeviceQualityandCompliance/ucm378183.hm.

[376] U.S. FOOD AND DRUG ADMIN., *Voluntary National Retail Food Regulatory Program Standards—September 2015*, https://www.fda.gov/Food/GuidanceRegulation/RetailFoodProtection/ProgramStandards/ucm245409.htm

[377] *See supra* notes _-_ and accompanying text.

Relatedly, using as models certain recently adopted provisions of the Patent Act and other statutes, Congress could include a sunset provision for the comparative-evaluation proposal.[378] For example, the FDA's authority could end five years from the day that the law takes effect unless Congress extends it. In addition, Congress could pass a statute structured in such a way as to give the FDA some regulatory flexibility as to its scope, and the agency could expand or contract its coverage as needed. In all, the goal is to test whether the proposal leads to salutary data generation, discourages sham changes, and aids in improving human health as intended.

V. OBJECTIONS

This Part briefly considers potential objections to the proposal, including legal, prudential, and practical challenges. Although this Part does not directly engage with potential political challenges, such as the impact of lobbying, it is hoped that answers to these objections might temper political opposition.

First, a challenger might contend that the statute authorizing the FDA to request comparative information constitutes a Fifth Amendment taking that devalues a patent right, or violates the First Amendment by compelling speech by brand companies.[379] The takings challenge will fail, however, even if the Orange-Book delisting form of the proposal is adopted because such a listing is a regulatory entitlement orthogonal to the patent system: a claim for an "exaction" of a property right will not lie because an Orange Book listing is not a part of the bundle of rights under a patent.[380] As for the compelled speech claim, the government may lawfully impose certain speech requirements (e.g., the placement of health warnings on product packaging) on firms when the content of the speech is factual and the requirement to speak is related to a substantial government interest.[381] Both prongs are easily satisfied here: the matter on the label relates to the data submitted to the FDA, and the government's missions to protect human health and foster an informed

[378] *See generally* SOFIA RANCHORDAS, CONSTITUTIONAL SUNSETS AND EXPERIMENTAL LEGISLATION (2015). For a recent example in the patent context, see Leahy-Smith America Invents Act, Pub L. No. 112-29, 125 Stat. 284, § 18(a)(3) (2011) (providing for sunsetting of so-called covered business method patent reviews).

[379] *Cf. supra* notes _-_ and accompanying text.

[380] *See* 35 U.S.C. § 154(a) (providing that the patent gives its owner a right to exclude others "from making, using, offering for sale, or selling the invention throughout the United States" for the length of the patent term).

[381] *See, e.g.*, CTIA—The Wireless Ass'n v. City of Berkeley, 854 F.3d 1105 (9th Cir. 2017); *cf.* Perry v. Sindermann, 408 U.S. 593, 597 (1972) (holding that the government cannot deny someone a benefit on a basis that infringers that person's freedom of speech).

marketplace should meet the substantial interest requirement based on the settled precedent. The proposed information-forcing mechanism is not unlike the mandate to note the drug indication on the label after the regular approval process, and it does not in any way limit truthful speech that brand companies may engage in as they advertise the product.[382]

Second, it may be argued that the proposal would discourage research into drug improvements and result in fewer extended release formulations, and the like, on the market. Although effects of proposed legislation are always difficult to predict, the aim of the proposal is not to keep modified drug forms off the market, but rather to help physicians and payers recognize potential sham changes and make their decisions accordingly. Data can of course be costly to generate, but the proposed standard provides for some relatively cheap ways, such as indirect comparisons, by which firms can meet the relevancy standard.[383] In addition, firms meeting that standard would have a freer hand to conduct comparative advertising and would not need to fear antitrust litigation. Increased transparency can thus benefit pharma companies in the market, in courts, and—not insignificantly—in the court of public opinion, perhaps offsetting the costs of producing and revealing drug information. Even if the costs for brands end up being too high, a socially undesirable outcome of reduced drug options is not a given. One, if the innovators do not fill the need for drug modifications, third parties could pick up the slack and supply the market without the onus of providing comparative data. Two, if the sunsetting version of the proposal is adopted and the framework is failing, the authority would simply not be extended. Finally, to the extent that "extensions" of exclusivity through secondary patenting are needed to provide an adequate effective length of protection for pioneering products,[384] the solution is to extend pioneering patent term to account for regulatory delay rather than encourage gaming of the sort that sometimes takes place with product hopping.[385]

The third set of concerns relates to the FDA's capacity to undertake the comparative analysis and the costs of the proposal. As to the former, because the FDA must already make comparative judgments between drug candidates in other contexts, such as priority reviews, such an exercise for closely related drug forms should be well within the agency's expertise.[386] Significantly, the proposal does not task the FDA's with engaging in cost-effectiveness analysis, which would push beyond

[382] *See supra* notes _-_ and accompanying text.
[383] *See supra* notes _-_ and accompanying text.
[384] *See supra* notes _-_ and accompanying text.
[385] *See generally* Dogan & Lemley, *supra* note 319.
[386] *See supra* notes _-_ and accompanying text.

the agency's core competency of analyzing scientific data toward territory into which it has historically been reluctant to enter.[387] Instead, the proposal asks only that the agency process and evaluate submitted data, and leaves cost-effectiveness decisions to payers and others. As to the latter, although the new authority would certainly increase pressures on the FDA, some of the added expense could be covered by outlays from the extensive CER budget.[388] Pre-approval comparative analysis can dovetail with CER conducted after the drug is marketed, driving initial drug adoption choices and supplying information for future research and thus justifying CER coverage. Even if the CER budget is unavailable for implementing the proposal, perhaps its costs would still be reasonable because comparative analysis would occur contemporaneously with, and rely on some of the same data as, regular approval, creating economies of scale for the agency. Finally, some of the expenses could be covered by user fees.[389]

Fourth, agency capture is a concern with any proposal that could confer a benefit on industry players. One response to this objection is that the FDA has traditionally been viewed as one of the least-captured agencies, driven by science and rarely accused of cultivating improper industry relationships or yielding to undue pressures. The ability of third parties that may be affected by comparative determinations, like generic companies, to file citizen petitions that challenge the FDA's decisions and are subject to judicial review, provides a further check on the agency.[390] And although the goal of this proposal is not to re-litigate the FDA's scientific judgments, egregious errors made by captured officials could be corrected by direct challenges under the Administrative Procedure Act[391] or perhaps in collateral antitrust litigation—though, of course, the goal of the proposal is to avoid the latter if possible. In addition, scholars have proposed various measures to combat capture, including stopping the revolving door between government and industry, if that becomes a serious problem.[392]

The various objections are, therefore, surmountable. In addition, recent statements from the Commissioner of Food and Drugs indicate some dissatisfaction with the agency's role in facilitating product

[387] *But see* David A. Hyman & William C. Kovacic, *Risky Business: Should the FDA Pay Attention to Pharmaceutical Prices?*, https://ssrn.com/abstracts=2970683 (making the case that the FDA should engage in economic cost-benefit analysis in some circumstances).
[388] *See supra* notes _-_ and accompanying text.
[389] *See* Prescription Drug User Fee Act, Pub. L. 102-571, 106 Stat. 4491 (Oct. 29, 1992).
[390] *See supra* note 324 and accompanying text.
[391] 5 U.S.C. §§ 551-559.
[392] *See, e.g.*, Rachel E. Barkow, *Insulating Agencies: Avoiding Capture Through Institutional Design*, 89 TEX. L. REV. 15 (2010).

hopping of the preventive kind and a desire to find a solution to this problem.[393] Although Dr. Gottlieb's recent activities include an exploration of a potential alliance with the FTC to deal with anticompetitive conduct,[394] the Commissioner has also shown interest in bolstering the FDA's own role in increasing transparency and competition in the pharmaceutical markets.[395] In addition, at a recent public hearing, an FDA official asked specifically whether a showing of a clinical benefit from a drug reformulation, such as increased patient compliance, would be a good idea.[396] The proposal, then, appears to be one that could be embraced by the agency, which could ease its implementation.

CONCLUSION

Not all pharmaceutical products are alike. Some are completely new drugs, while others are incremental modifications of drugs already on the market. Both have value in their own right, but the goals with the latter are often much clearer: to better the pioneering drug in some specific dimension, such as improving patient compliance or reducing side effects. Sometimes, however, product changes coupled with follow-on patents can embody a strategy that is focused mainly on attempting to maintain the brand's exclusivity rather than advancing the quality of patient care and human health. The proposal in this Article enlists the FDA in the effort to encourage the latter—which, after all, is why the pharmaceutical industry exists in the first place.

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[393] *See supra* notes _-_ and accompanying text.

[394] *See* FED. TRADE COMM'N, *Understanding Competition in Prescription Drug Markets: Entry and Supply Chain Dynamics*, https://www.ftc.gov/news-events/events-calendar/2017/11/understanding-competition-prescription-drug-markets-entry-supply (Nov. 8, 2017).

[395] Scott Gottlieb, M.D., U.S. FOOD AND DRUG ADMIN.: FDA VOICE BLOG, *Reducing the Hurdles for Complex Generic Drug Development* (Oct. 2, 2017), https://blogs.fda.gov/fdavoice/index.php/2017/10/reducing-the-hurdles-for-complex-generic-drug-development.

[396] *See* Statement by Kathleen Uhl, M.D., FDA ("When you were talking about post-approval changes, you said about the ability to improve tolerability, adherence—I believe you had four specific examples that you used. So my question is should there be a requirement to demonstrate any or all four of those when the agency approves any postmarketing type changes to the innovator?") (quoted in Comment from Pharmaceutical Research and Manufacturers of America (PhRMA) at 18 n.87, *Administering the Hatch-Waxman Amendments: Ensuring a Balance Between Innovation and Access*, Docket FDA-2017-N-3615 (Nov. 20, 2017), https://www.regulations.gov/document?D=FDA-2017-N-3615-0108). The other two examples were convenience and efficacy. *Id.*