THE MORE THINGS CHANGE:

IMPROVEMENT PATENTS, DRUG MODIFICATIONS, AND THE FDA

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Abstract

Pharmaceutical companies often replace prescription drugs that are already on the market with modified versions that have the same active pharmaceutical ingredient. On the surface, such activity seems benign and perhaps even salutary. Nonetheless, antitrust litigation has revealed that firms sometimes modify existing drugs not because new formulations would demonstrably improve health outcomes, but principally because so-called secondary patents covering the new version of the drug enable them to maintain some effective market power over the active ingredient for which primary patent protection has expired. This "product-hopping" strategy runs counter to the goal of the legislative framework for regulating branded and generic drug approvals, which is to create appropriate incentives for discoveries that raise the quality of patient care and human health by providing a period of reward for the brand followed by timely and effectual generic entry.

In this Article, I explain that the rules and institutions involved in determining the validity of patents on chemical inventions, certain features of drug regulation under the Federal Food, Drug, and Cosmetic Act, and unique market forces in the pharmaceutical sector combine to allow strategic product hopping. To address this problem, I propose a novel regulatory scheme that would empower the Food and Drug Administration (FDA) to induce pharmaceutical companies to generate comparative data indicative of therapeutic distinctiveness 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 show that the relevant information can be presented in a manner that is useful to patients, prescribers, and payers. The proposed framework would then enable these market participants to identify and reject strategic drug product changes, reducing the manufacturer's incentive to pursue such modifications. Ultimately, the FDA's new authority for comparative data development could 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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TABLE OF CONTENTS

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 scorn for keeping the prices of some of those drugs very high and occasionally engaging in questionable business practices.[2] As one commentator has noted, "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 the pharmaceutical industry 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 lead to calls for governmental interventions.

One 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 over that product from other manufacturers, thanks to patents covering the drug.[8] As these "primary" or "pioneering" patents approach expiration, the company obtains new patents covering the drug's modification—for example, so-called

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[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); *see also* New York *ex rel.* Schneiderman v. Actavis PLC, 787 F.3d 638, 643 n.2 (2d Cir. 2015); Michael A. Carrier & Steve D. Shadowen, 92 NOTRE DAME L. REV. 167, 168-69 (2016) (calling this phenomenon a "price disconnect").

[8] Although FDA-approved drug products can also be supported by non-patent exclusivities, product-hopping is most often tied to patent expiration followed by new patenting. *See infra* notes 63-65 and accompanying text.

"extended-release" tablets—and secures a separate FDA approval for this version.[9] The company then begins to advertise the new product heavily, while deemphasizing the one that is about to go off-patent.[10] In the more aggressive cases, the brand company might disparage the original version or even take it completely off the market, thereby forcing a switch to the modification.[11]

After the patents covering the pioneering product expire, other companies—after undergoing their own, shortened FDA approval processes—can offer "copies" of the original product as relatively cheap, "generic" alternatives pursuant to the provisions of the Federal Food, Drug, and Cosmetic Act (FDCA).[12] This regime is reinforced by generic substitution laws, adopted in some form in every state, which essentially authorize pharmacists to supply patients with a generic version of a drug even when physicians prescribe the more expensive brand.[13] But a product-hopping strategy can render the original, off-patent form of the drug obsolete and cause a permanent shift to the newly patented, more expensive modification.[14] Due to various defects in the market for prescription drugs, these follow-on versions may—and have—achieved significant penetration without credible evidence of any kind of therapeutic improvement over, or even meaningful clinical difference

[9] For a leading example from the case law, see *Actavis*, 787 F.3d 638. Extended-release versions of drugs differ from their immediate-release counterparts in that—as the two terms suggest—the former are, generally speaking, engineered so as to discharge the active pharmaceutical ingredient (i.e., the working part of the drug) into the bloodstream more slowly than the latter. *See, e.g.*, Ali Nokhodchi et al., *The Role of Oral Controlled Release Matrix Tablets in Drug Delivery Systems*, 2 BIOIMPACTS 175 (2012).

[10] *See, e.g.*, *In re* Asacol Antitrust Litig., 15-cv-12730-DJC, 2016 WL 4083333, at *2-3 (D. Mass. July 20, 2016); Walgreen Co. v. AstraZeneca Pharm. L.P., 534 F. Supp. 2d 146, 150-52 (D.D.C. 2008).

[11] *See, e.g.*, *Actavis*, 787 F.3d at 647-49; *In re* Loestrin 24 Fe Antitrust Litig., 261 F. Supp. 3d 307, 349-54 (D.R.I. 2017); *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); *see also Asacol*, 2016 WL 4083333, at *3.

[12] *See* 21 U.S.C. § 355(j); *see generally* 52 Stat. 1040 (1938), *codified at* 21 U.S.C. § 301 *et seq.*

[13] *See infra* notes 120-125 and accompanying text (describing the varieties of generic substitution laws); *see also* 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).

[14] The generic, however, does not lose the approval to market the "copy" when the brand has pulled the product from the shelves—unless that had to be done for safety or effectiveness reasons. 21 C.F.R. § 314.122(a) (2018).

from, their predecessors.[15] Some have argued, therefore, that product hops can contribute to drug prices that are unnecessarily high.[16]

Some product hops, particularly those involving so-called "forced" or "hard" switches—terms that refer to removal of the original product from the market—have prompted antitrust challenges. In one well-known case, *New York ex rel. Schneiderman v. Actavis PLC*, the Court of Appeals for the Second Circuit upheld a district court's determination that the defendant brand pharmaceutical company likely violated § 2 of the Sherman Act, which prohibits actual or attempted single-firm monopolization.[17] This conclusion was based in part on a finding that the company stopped selling a pioneering version of an Alzheimer's drug called Namenda shortly before patents covering it expired and replaced it with a follow-on purely for strategic reasons.[18] Specifically, the record revealed that the firm engineered the switch from the immediate-release (IR) to the extended-release (XR) version of Namenda so as to prevent generic entrants from gaining market share that would have been possible thanks to patent expiration and generic substitution.[19]

The court determined that, having been compelled to make the switch once, physicians would be unwilling to revert to the cheaper generic due to the sensitivity of the Alzheimer's patient population to continued shifts in their therapeutic regimens.[20] In addition, the court noted that constraints associated with the generic companies' business model—which depends on generic substitution rather than marketing—would make it difficult for generics to "cost-efficient[ly]" convince prescribers and patients to re-adopt the pioneering form of the drug in any

[15] *See, e.g.*, Peter Mansfield et al., *Single-Enantiomer Drugs: Elegant Science, Disappointing Effects*, 42 CLIN. PHARMACOKINETICS 287, 287 (2004) ("Patent protection and a perception of superiority based on promotion rather than evidence will maintain price premiums for single enantiomer drugs that are not justified on the basis of clinical performance."); *see also* Ismayil Ahmet et al., *Fenoterol Enantiomers do not Possess Beneficial Therapeutic Properties of Their Racemic Mixture in the Rat Model of Post Myocardial Infarction Dilated Cardiomyopathy*, 26 CARDIOVASCULAR DRUG. THER. 101 (2012); 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). *But see, e.g.*, Pascal Auquier et al., *Comparison of escitalopram and citalopram efficacy: A meta-analysis*, 7 INT'L J. PSYCHIATRY CLIN. PRACTICE 259 (2003) (providing a counterexample).

[16] Aaron S. Kesselheim et al., *The High Cost of Prescription Drugs in the United States: Origins and Prospects for Reform*, 316 J. AM. MED. ASS'N 858 (2016).

[17] 15 U.S.C. § 2 (2018).

[18] *Actavis*, 787 F.3d at 658-60. The court concluded that the plaintiff was likely to succeed on both monopolization and attempted monopolization claims. *Id.* at 651, 660.

[19] *Id.* at 654, 658.

[20] *Id.* at 656.

event.[21] But the switch may have necessitated these inefficient marketing outlays after generic entry because, although no clinical difference between old and new forms of Namenda was demonstrated,[22] pharmacists could not legally give patients the former when doctors prescribed the latter because the shift to the XR form precluded the application of generic substitution.[23] Consequently, after faulting the brand 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,"[24] the court upheld a preliminary injunction ordering the company to continue selling the original, immediate-release form of the drug.[25]

As a matter of antitrust doctrine, "product hopping" monopolization theories have drawn a mixed reception from commentators. Some have praised the Second Circuit for providing a remedy against conduct that appears to thwart the regulatory frameworks intended to foster cost savings from the introduction of generic drugs.[26] Others, however, have criticized the court's approach for arrogating to the judiciary the power to police pharmaceutical product markets and even giving courts a seemingly unsuitable task of comparing benefits of different drug products.[27] Later decisions have followed *Actavis* with some caution, allowing antitrust claims to proceed in hard switch scenarios based on ostensible "consumer coercion,"[28] but generally

[21] *Id.* a 655.
[22] *See infra* notes 264-268 and accompanying text
[23] *See infra* notes 131-132 and accompanying text. *But cf.* Arti K. Rai & Barak D. Richman, *A Preferable Path for Thwarting Pharmaceutical Product Hopping*, HEALTH AFF. BLOG (May 22, 2018) (setting forth an approach that would lead to permissible generic substitution in such circumstances), https://www.healthaffairs.org/do/10.1377/hblog20180522.408497/full.
[24] *Actavis*, 787 F.3d at 659 (emphasis added). By "reformulated" here, the Second Circuit is of course not referring to a change in an inactive ingredient that does not affect the original drug. Instead, the reformulation has led to a change in dosing, resulting in a "new drug" under the FDCA. *See infra* notes 128-132 and accompanying text.
[25] Before finding an antitrust violation, the court had to determine the relevant market, which it concluded to be memantine. *Id.* at 646-52; *cf.* Mylan Pharm. Inc. v. Warner-Chilcott PLC, 838 F.3d 421 (3d Cir. 2016) (finding no monopolization or attempted monopolization where there were other drugs available in the relevant market and, since the defendant had no dominant market position with the respect to the product at issue, no antitrust violation).
[26] *See, e.g.*, ROBIN FELDMAN & EVAN FRONDORF, DRUG WARS: HOW BIG PHARMA RAISES PRICES AND KEEPS GENERICS OFF THE MARKET 69-78 (2017); Carrier & Shadowen, *supra* note 7; *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).
[27] *See, e.g.*, Douglas H. Ginsburg et al., *Product Hopping and the Limits of Antitrust: The Danger of Micromanaging Innovation*, COMPETITION POL'Y INT'L ANTITRUST CHRON., Dec. 2015, at 1; Joanna Shepherd, *Deterring Innovation:* New York v. Actavis *and the Duty to Subsidize Competitors' Market Theory*, 17 MINN. J.L. SCI. & TECH. 663 (2016).
[28] *See, e.g. In re* Loestrin 24 Fe Antitrust Litig., 261 F. Supp. 3d 307 (D.R.I. 2017).

dismissing cases in which plaintiffs alleged only a "soft switch"—that is, when defendants deemphasized the old product but did not actually withdraw it from the market.[29]

Thus, courts have been unwilling to use antitrust law to broadly condemn product-hopping practices, perhaps out of concern that doing so might put them into an awkward quasi-regulatory role.[30] Indeed, although antitrust can have an important function even in a highly regulated industry such as pharmaceuticals,[31] decisions from the Supreme Court have recognized that in deciding whether to impose antitrust liability, "careful account must be taken of the pervasive federal and state regulation characteristic of the industry."[32] To be sure, an antitrust intervention may well be warranted when a regulatory regime is not "an effective steward of the antitrust function."[33] But even if this is so, a question worth asking is whether the regime can be fixed so as to reduce ex ante the prevalence of conduct that might otherwise draw antitrust scrutiny and to avoid enlisting courts as ex-post fixers of regulatory flaws.[34] Moreover, substantive, procedural, and practical constraints on

[29] *See, e.g.*, *Mylan Pharm.*, 838 F.3d 421.

[30] *See* Hillary Greene, *Muzzling Antitrust: Information Products, Innovation and Free Speech*, 95 B.U. L. REV. 35, 77-78 (2015) (noting that, as a matter of practice, antitrust courts rarely engage in balancing of pro-competitive benefits versus anti-competitive harms of innovation); *cf.* John M. Newman, *Anticompetitive Product Design in the New Economy*, 39 FLA. ST. U. L. REV. 681 (2012) (arguing that certain product redesigns should and do give rise to viable antitrust claims).

[31] *See generally* Stacey L. Dogan & Mark A. Lemley, *Antitrust Law and Regulatory Gaming*, 87 TEX. L. REV. 685 (2009).

[32] Verizon Commc'ns Inc. v. Law Offices of Curtis V. Trinko, LLP, 540 U.S. 398, 411 (2004) (quoting United States v. Citizens & Southern Nat. Bank, 422 U. S. 86, 91 (1975)).

[33] *Id.* at 413.

[34] *See* Dennis W. Carlton et al., *Does FTC's Theory of Product-Hopping Promote Innovation?*, 21. J. COMPETITION L. & ECON. 495, 503 (2016) (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"); Alan Devlin & Michael Jacobs, *Anticompetitive Innovation and the Quality of Invention*, 27 BERKELEY TECH. L.J. 1, 51 (2012) ("[P]olicymakers should not distort well-established antitrust rules in order to solve what is, at heart, a regulatory problem."); 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 in 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); *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). *Cf. generally* C. Scott Hemphill, *Paying for Delay: Pharmaceutical Patent Settlement as a Regulatory Design Problem*, 81 N.Y.U. L. REV. 1553 (2006); Jacob S. Sherkow, *Administrating Patent Litigation*, 90 WASH. L. REV. 205, 214-15, 250-253 (2015) (calling for a greater role for the FDA to police certain conduct by owners of pharmaceutical patents).

antitrust actions further limit meaningful and timely inquiry into whether a product hop was problematic.[35]

But what precisely is the problem prompting the need for a regulatory fix? A business model based on the strategy of product substitution seemingly for its own sake, with no demonstrated clinical distinction from the original, presents an issue of potential public concern that the antitrust cases have uncovered. In *Actavis*, for example, the defendants' CEO stated that "[w]e need to transition volume to XR to protect our Namenda revenue from generic penetration in 2015 when we lose IR patent exclusivity."[36] In another case, *In re Asacol*, it was alleged that the brand engineered an "unnecessary modification" that ended up making the new version of the drug tougher to swallow for some patients and undertook a soft, and then hard, switch away from the more convenient original to the more expensive follow-on.[37]

To some of the more transparently strategic hops of this sort, prescribers and patients have responded by largely continuing to use the original—at least until the hard switch.[38] But in other cases, significant shifts to new and more expensive products took place without any data that might justify the change.[39] Such shifts can occur because of information gaps and other flaws in the market for pharmaceuticals, to be discussed throughout the Article,[40] that antitrust law probably cannot fully correct.[41] Thus, leaving aside the threat of antitrust liability in particularly aggressive cases, incentives are in place for firms to modify existing products without also developing evidence tending to show whether the change might make sense for patients.

The statutory frameworks that have pushed some pharmaceutical companies toward strategic product hopping encompass patent law and food and drug law. Patents are powerful rights whose acquisition does

[35] *See* 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 Actavis] properly prompt antitrust disputes, the need for such actions may still result in a delay in generic competition"); Rai & Richman, *supra* note 23.
[36] New York *ex rel.* Schneiderman v. Actavis PLC, 787 F.3d 638, 658 (2d Cir. 2015).
[37] *In re* Asacol Antitrust Litig., 15-cv-12730-DJC, 2016 WL 4083333, at *4-5 (D. Mass. July 20, 2016).
[38] *Id.*
[39] *See* Mansfield et al., *supra* note 15; *see also* Walgreen Co. v. AstrsaZeneca Pharm. L.P., 534 F. Supp. 2d 146, 147-49 (D.D.C. 2008).
[40] *See especially infra* Part III.
[41] See STEPHEN G. BREYER, A THEORY OF REGULATION 26-28, 159-64 (1982); *see also* Howard A. Shelanski, *Justice Breyer, Professor Kahn, and Antitrust Enforcement in Regulated Industries*, 100 CALIF. L. REV. 487, 494 (2012) ("Breyer . . . identified several regulatory tasks for which antitrust would be inadequate, notably the correction of moral hazard and information asymmetry problems . . . .").

not, generally speaking, require a showing of clinical improvement, or even distinctiveness, when an existing drug is modified.[42] For example, the utility requirement of § 101 of the Patent Act does not demand that the applicant show that the new invention is in any way better or more useful than what is already available,[43] and the requirement that a patent claim be non-obvious under § 103 focuses mainly on whether the claim embodies a sufficiently inventive cognitive leap over what is in the public domain.[44]

Somewhat in tension with these aspects of patent doctrine,[45] results made possible by the patented invention that were unexpected in view of what was known in the field (e.g., the therapeutic profile of the previous version of the drug),[46] as well as other types of evidence that might stand in for improvements in patient care, can and do come into the non-obviousness analysis.[47] But patent applications are filed early in the research process[48]—before much, if any, comparative data that can speak usefully to these issues have been developed.[49] Thus, the combination of established doctrinal rules and the often limited quality of the data available during the patent acquisition process (the official term for it is "patent prosecution") ensures that examiners at the U.S. Patent and

[42] *See, e.g.*, *In re* Sichert, 566 F.2d 1154 (C.C.P.A. 1977); *see also* Scott v. Finney, 34 F.3d 1058 (Fed. Cir. 1994).
[43] *See* Lowell v. Lewis, 15 F. Cas. 1018, 1019 (C.C.D. Mass. 1817) (No. 8568) (Story, Circuit Justice); *see also* ROBERT PATRICK MERGES & JOHN FITZGERALD DUFFY, PATENT LAW AND POLICY: CASES AND MATERIALS 201 (7th ed. 2017); Carrier & Shadowen, *supra* note 7, at 181. *See generally* W. Nicholson Price II, *The Cost of Novelty* (on file with author).
[44] Graham v. John Deere Co. of Kan. City, 383 U.S. 1, 17-18 (1966); Custom Accessories, Inc. v. Jeffrey-Allan Indus., Inc., 807 F.2d 955, 960 n.12 (Fed. Cir. 1986); *see* 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). *See generally* Michael B. Abramowicz & John F. Duffy, *The Inducement Standard of Patentability*, 120 YALE L.J. 1590 (2011).
[45] *See infra* Part II.B.
[46] *See, e.g.*, *In re* Merchant, 575 F.2d 865 (C.C.P.A. 1978); *see also* Tamsen Valoir, *Six Methods of Preserving Market Exclusivity*, 18 INTELL. PROP. & TECH. L.J. 12 (2006) ("[R]esearchers may *plan ahead* to collect comparative data, showing that the improved product has unexpected advantages over the product disclosed in the original application. Thus, a particular species of drug with a particular activity level might be patentable, even though the genus of drugs was disclosed earlier. Any showing of unexpected advantages can be used to counter an obviousness rejection, and incorporating follow-on applications into a patent strategy early will allow scientists to design their research path accordingly." (emphasis in original)).
[47] *Graham*, 383 U.S. at 17-18 (discussing secondary considerations); *see also* Arctic Cat Inc. v. Bombardier Recreational Prods. Inc., 876 F.3d 1350, 1358-59 (Fed. Cir. 2017).
[48] *See generally* Ted Sichelman, *Commercializing Patents*, 62 STAN. L. REV. 341 (2010); *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).
[49] *See* Jonathan J. Darrow, *Pharmaceutical Gatekeepers*, 47 IND. L. REV. 403 (2014).

Trademark Office (PTO) do not see a full clinical picture of the difference between pioneering drugs and follow-on versions.[50]

To be sure, assuming the patent issues, the picture might become somewhat more complete by the time the validity of the patent is litigated in court.[51] And while some of the newly developed evidence can bolster the case for patentability,[52] the adversarial process can also reveal flaws in prosecution and lead to the patent's invalidation.[53] Indeed, litigation between brand and generic companies results in invalidation of patents covering follow-on drugs with some frequency,[54] allowing the generic entrants to make and sell the follow-on version. The brand-generic litigation process, however, can take up a significant amount of time until the issues of generic company liability are finally resolved.[55] Thus, even if the generics ultimately succeed in invalidating the asserted patents, the brand effectively enjoys a period of erroneously granted exclusivity while those patents are still in force.[56] This is yet another feature of the

[50] *See* Rebecca S. Eisenberg, *Pharma's Nonobvious Problem*, 12 LEWIS & CLARK L. REV. 375, 395-36 (2008); *see also* Greg Reilly, *Decoupling Patent Law*, 97 B.U. L. REV. 551, 577 (2017) ("In practice, secondary considerations are rarely relied on during patent acquisition both because of the difficulty for examiners in identifying and developing evidence of real world activities (as opposed to printed materials) and because secondary considerations tend to be ex post factors that only arise after the patent is granted and the invention publicized and marketed.").

[51] *See infra* notes 178-181 & 216-222 and accompanying text (discussing the Seroquel example).

[52] *See id.*

[53] *Cf. generally* Mark A. Lemley, *Rational Ignorance in the Patent Office*, 95 NW. U. L. REV. 1495 (2001).

[54] *See* C. Scott Hemphill & Bhaven N. 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" of the PTO is responsible for the highest percentage of invalidated patents of all the art units). Although selection effects certainly influence the rate of invalidation, the fact remains that there is a significant number of erroneously granted patents in the pharmaceutical space.

[55] Challenges to patentability at the Patent Trial and Appeal Board (PTAB), however, can lead to relatively quick invalidations—assuming the challenger can get past the hurdle of the PTO's discretionary institution of a post-issuance review. *See* Joanna Shepherd, *Disrupting the Balance: The Conflict Between Hatch-Waxman and Inter Partes Review*, 6 N.Y.U. J. INTELL. PROP. & ENT. L. 14, 37 (2016).

[56] *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), *rev'g*, Bayer Schering Pharma AG v. Watson Pharm., Inc., Nos. 2:07-CV-01472-KJD-GWF, 2:08-CV-00995-KJD-GWF, 2012 WL 1079551; and Bayer Schering Pharma AG v. Lupin Ltd., No. 2:10-CV-01166-KJD-RJJ2012 WL 1080296 (D. Nev. Mar. 30, 2012). As part of the reversal, the Federal Circuit concluded that the district court erred in crediting the patentee's unexpected results evidence. *Id.* at 1377; *cf. Bayer*, 2012 WL 1079551, at *21-22 ("[T]he undisputed evidence demonstrates three unexpected results of Bayer's invention."). The Federal Circuit, to be sure, granted an emergency stay of the district court's injunction against one of the defendants' ANDA approvals in a related appeal a month prior issuing the decision reversing the judgment that the patents are not invalid. *See* Order, Bayer Healthcare Pharm., Inc. v. Sandoz, Inc., No. 13-1207 (Fed. Cir. Mar. 13, 2013), ECF No. 57.

regulatory mix that can make patents the paramount inducer of drug reformulation efforts. Finally, it bears emphasizing that even if the decision-makers were to have perfect and timely evidence before them and could make patentability decisions with a high degree of accuracy, the fact remains that the relationship between non-obviousness and relative product quality is not a straightforward one as a matter of substantive patent law.[57]

For its part, the FDA generally does not evaluate comparative advantages or disadvantages of new drug versions—and brand companies, sometimes referred to as "sponsors," do not have to obtain such information and provide it to the agency.[58] Modified drugs,[59] like all others, are generally governed by the standard approval requirement of proof of safety and efficacy[60] over a placebo.[61] Indeed, the agency

[57] *See infra* Part II.B; *see also* Janice M. Mueller & Donald S. Chisum, *Enabling Patent Law's Inherent Anticipation Doctrine*, 45 HOUS. L. REV. 1101, 1156-57, 1163-64 (2008) (explaining why another patent law doctrine, inherent anticipation, is ill-suited to address strategic behavior by brand pharmaceutical companies).

[58] See Carrier & Shadowen, *supra* note 7; Amy Kapczynski & Talha Syed, *The Continuum of Excludability*, 122 YALE L.J. 1900, 1956 & n.180 (2013); Russell Korobkin, *Comparative Effectiveness Research as Choice Architecture: The Behavioral Law and Economics Solution to the Health Care Cost Crisis*, 112 MICH. L. REV. 523, 550-51 (2014). For suggestions to incorporate comparative effectiveness analysis in the FDA approval process, see G. Caleb Alexander & Randall S. Stafford, *Does Comparative Effectiveness Have a Comparative Edge?*, 301 J. AM. MED. ASS'N 2488, 2488 (2009); Alec B. O'Connor, *Building Comparative Efficacy and Tolerability into the FDA Approval Process*, 303 J. AM. MED. ASS'N 979 (2010). For a proposal to make comparative efficacy a general requirement of drug approvals in Europe, see Corinna Sorenson et al., *Evidence of comparative efficacy should have a formal role in European drug approvals*, 343 BRITISH MED. J. 514 (2011).

[59] To be sure, the FDA treats modifications involving a change in dosage formally as new drugs. *See infra* Part I.

[60] *See* 21 U.S.C. § 355(b). As part of this requirement, the sponsor has to provide "evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof." *Id.* § 355(d). To support this claim, the sponsor must submit "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). Although those terms are often used interchangeably, the 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. RES. SERV., RL34208, COMPARATIVE CLINICAL EFFECTIVENESS AND COST-EFFECTIVENESS RESEARCH: BACKGROUND, HISTORY, AND OVERVIEW 4 (2007). Nonetheless, pre-approval studies can, subject to various qualifications due to their limitations, provide the kinds of results that allow such studies to serve as proxies for effectiveness in actual clinical practice. *See 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).

[61] *See* 21 C.F.R. § 314.126(b) (2018) (setting forth placebo and no-treatment controls as sufficient for meeting the statutory requirements for approval). There are some exceptions. *See, e.g.*, *Non-*

typically does not ask the sponsor to provide any data suggestive of clinical distinctiveness between a drug's new form and the previous one, and such data is often completely unavailable when the new version enters the market.[62] The FDA does have at its disposal some exclusivity mechanisms that could encourage and reward sponsor studies generating information of potential relevance to comparative safety and efficacy of the two drug versions.[63] However, the lengthy term of patent protection and regulatory benefits that come with drug patents[64] can dwarf any reward that the FDA is currently empowered to provide.[65] As a result, exclusivities based on the submission of data to the FDA can be rendered unnecessary for brand companies that have obtained patents covering reformulated products.

Given these features of the Patent Act and the FDCA, therefore, drug product changes can sometimes be driven not by increased clinical benefits or even clinical distinctiveness, but principally by the possibility of obtaining patent protection for the drug's new version.[66] This is unfortunate because incremental pharmaceutical innovation, if properly channeled,[67] can be crucial for health outcomes.[68] Sometimes, for

Inferiority Clinical Trials to Establish Effectiveness: Guidance for Industry, U.S. FOOD AND DRUG ADMIN. (Nov. 2016), https://www.fda.gov/downloads/Drugs/Guidances/UCM202140.pdf.

[62] *See* 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."). Sometimes, a sponsor does make certain comparisons, but they end up not being relevant to any kind of demonstrable distinctiveness between the two products. *See infra* notes 264-265 and accompanying text (discussing comparative experiments performed for Namenda IR and XR); *cf.* Jitendra Ganju & Dror Rom, *Non-inferiority versus superiority drug claims: the (not so) subtle distinction*, 18 TRIALS 278 (2017) (contrasting statistical and clinical superiority).

[63] *See, e.g.*, *id.* § 355(c)(3)(E)(iii)-(iv) (providing for a three-year market exclusivity for drug modifications for which the sponsor conducted certain new clinical investigations essential to approval). This exclusivity, however, does not require comparative analysis.

[64] *See infra* Part I (discussing benefits that *Orange Book* listings provide).

[65] This discussion assumes that so-called "secondary" patents have terms extending significantly beyond the expiration of the terms of so-called "primary" patents, a scenario that often holds in practice. For a discussion of primary and secondary patents, *see infra* Part II.

[66] 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).

[67] *See* Mueller & Chisum, *supra* note 57, at 1106 n.12 ("Drawing the line between improper attempts at evergreening and legitimate incremental innovation is a broad and difficult problem in patent law . . . ."). "Evergreening" is a potentially pejorative term that refers to practices that include strategic product hopping. *See* JOHN R. THOMAS, CONG. RES. SERV., R40917, PATENT "EVERGREENING": ISSUES IN INNOVATION AND COMPETITION 1 (2009); *see also supra* note 54 and accompanying text; *infra* note 482 and accompanying text.

[68] Joshua Cohen & Kenneth Kaitin, *Follow-on Drugs and Indications: The Importance of Incremental Innovation to Medical Practice*, 15 AM. J. THERAPEUTICS 89 (2008); Linda Simoni Wastila et al., *World Health Organization's essential drug list. The significance of me-too and*

example, extended-release formulations can provide the same therapeutic benefit from a smaller number of tablets than immediate-release, which can in turn help increase patient compliance.[69] Moreover, such modifications can offer 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.[70] But for certain drugs, extended-release versions could also exhibit *reduced efficacy* compared to their immediate-release counterparts,[71] potentially without offering any demonstrated compliance or other benefits.[72] Comparative evidence, therefore, can play a critical role of informing the market by demonstrating advantages or disadvantages of the new drug version over the old.

In general, motivations for modifying existing drugs can be straightforward enough to state—to better the pioneering drug in some specific dimension, such as improving compliance, ameliorating side effects, and so on. Nonetheless, as noted,[73] the sponsor does not have to actually demonstrate to the FDA that the modification would offer any of those advantages generally, or even for some particular patient sub-population. Furthermore, the fact that comparative premarket data that may counsel for or against a drug switch is lacking can be obscured by forceful advertising, which can deepen the aforementioned information gaps.[74] To the extent that courts and litigants may help bridge them through antitrust law,[75] they can only do so some time after the modified product was introduced. More importantly, given the coercion rationale,

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follow-on research, 3 J. CLIN. RES. & DRUG. DEV. 105 (1989); Albert I. Wertheimer & Thomas M. Santella, *Pharmaceutical Evolution: The Advantages of Incremental Innovation in Drug Development*, COMPETITIVE ENTERPRISE INSTITUTE (Apr. 2009), http://cei.org/sites/default/files/Wertheimer%20and%20Santella%20-%20Pharmaceutical%20Evolution.pdf; *see also infra* note 331 and accompanying text (providing specific examples).

[69] *See, e.g.*, 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); *see also* Nokhodchi, *supra* note 9, at 176.

[70] Nokhodchi, *supra* note 9, 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); *see also* Gilbert Block et al., *Comparison of Immediate-Release and Controlled Release Carbidopa/Levodopa in Parkinson's Disease*, 37 EUR. NEUROL. 23 (1997).

[71] *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 that can be introduced when drugs are modified).

[72] *See id.*

[73] *See supra* notes 58-62 and accompanying text.

[74] *See infra* Part III.

[75] *But cf.* BREYER, *supra* note 41, at 159-64 (expressing doubts about antitrust law's role as a tool for bridging information gaps, and favoring regulation for fixing such problems).

only the hard switch scenario has been found actionable[76]—so antitrust has so far played little if any information-forcing role in soft-switch cases. Thus, even if antitrust law were an effective tool for comparing benefits of drug products and fixing information gaps,[77] the timing of the inquiry and the focus on coercion limit antitrust's role in this area.

Although the FDA appears to lack the authority to request comparative data from sponsors,[78] its value and importance have not been lost on FDA officials. In a speech to the Controlled Release Society made in 1993, Dr. David Kessler, then the Commissioner of Food and Drugs, exhorted his audience to "[t]hink in terms of clinical outcomes. Demonstrated, documented, and rigorously established improvements to patient care."[79] At a public meeting in 2017, Dr. Kathleen Uhl, the Director of the FDA's Office of Generic Drugs, asked an industry representative whether a showing of a clinical benefit from a drug modification, such as increased patient compliance, would be a good idea.[80]

There may be some indirect authority that does allow the FDA to weigh in on such matters: for example, one fairly obscure provision of the FDCA empowers the agency to respond to PTO requests "to furnish full and complete information with respect to such questions relating to drugs as the Director may submit concerning any patent application."[81] Although the PTO has apparently never taken advantage of this subsection, it theoretically allows for FDA vetting of comparative data that a drug company submitted *to the PTO* in an effort to establish the patentability of a claimed formulation, perhaps under the "unexpected results" theory.[82] This provision even states that "[t]he Secretary is further authorized, upon receipt of any such request, to conduct or cause

[76] *See supra* notes 20-29 and accompanying text.
[77] *See supra* notes 30-35 and accompanying text.
[78] *Cf. infra* Part IV.D (exploring some possible sources of such authority in the current statute).
[79] Kessler, *supra* note 71, at 348.
[80] *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 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 of improvements that the industry representative gave were convenience and efficacy. *Id.*
[81] 21 U.S.C. § 372(d). *See* Darrow, *supra* note 49, at 402 ("The stated purpose of § 372(d), as described in the accompanying 1962 Senate Report, was unambiguously to reduce the number of patents issued on therapeutically questionable drugs.").
[82] *See supra* notes 46-47 and accompanying text; *see also* Darrow, *supra* note 49, at 401-02.

to be conducted, such research as may be required"[83]—a power that the PTO most certainly does not have.

Nonetheless, leaving aside the inherent challenges of generating comparative information given early patent filings, one wonders if this subsection's apparent goal to enlist the FDA in the task of examining pharmaceutical improvements might be better served by another mechanism enabling the FDA to request and analyze the data directly. In a sense, we currently have it backwards: instead of the FDA, it is the PTO, which is "a primarily technical agency with expertise in invention but not in the clinical trials that produce evidence of efficacy,"[84] that is charged with the responsibility of analyzing the information (if any) on the relative utility of the new form of the drug.[85] Although the legal questions that the two agencies ask are different, the ultimate goal of their respective efforts in the pharmaceutical space is improved quality of health care. Given that information relating to differences in clinical effect between two related drug products is clearly relevant to this general goal, it is surprising that the FDA—the agency with particular expertise in data analysis—is sidelined when it comes to such comparisons.

In this Article, I argue that rather than rely mainly on the backstop of antitrust litigation, completely rework patent law or patent institutions, or leave the matter exclusively to market forces, policymakers should consider addressing the phenomenon of product hopping through FDA-administered information-forcing strategies. At present, drug modifications are driven largely by the carrot of patentability,[86] but the regulatory mix lacks an effective stick against firms that undertake drug

[83] 21 U.S.C. § 372(d).

[84] Darrow, *supra* note 49, at 401.

[85] *See, e.g.*, *In re* Carabateas, 345 F.2d 1013, 1017 (C.C.P.A. 1965) (explaining in an appeal from the PTO that, "[w]hen considering that minor advances in activity are eagerly sought in pharmaceutical chemistry, a showing of nine and six times more activity than the most active compound of the art is indeed most significant, representing a different order of magnitude, and is proof of unobviousness and unexpected beneficial properties in a new compound"). In theory, courts deciding antitrust cases might also engage in comparative product analysis, though they rarely do so in practice. *See supra* note 30 and accompanying text.

[86] *Cf.* Gregory Dolin, *Exclusivity Without Patents: The New Frontier of FDA Regulation of Genetic Materials*, 98 IOWA L. REV. 1399 (2013) (proposing FDA-regulatory instead of patent-based mechanisms for incentivizing certain inventions); Yaniv Heled, *Patents vs. Statutory Exclusivities in Biological Pharmaceuticals—Do We Really Need Both?*, 18 MICH. TELECOMM. & TECH. L. REV. 419 (2012) (proposing a reduced emphasis on patents in setting exclusivity periods for so-called "biologics," or large-molecule drugs); *see also* Daniel J. Gervais, *Patents Are Optional* (on file with author). *See 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 FDA-administered exclusivities have come to play a bigger role than patent protection in incentivizing pharmaceutical innovation).

changes that are, at best, questionable in terms of their marginal clinical benefits.[87]

A mild version of a potential regulatory remedy for this omission could simply take the form of FDA requests that brand firms submit comparative premarket drug data that would be relevant to prescriber decisions.[88] If the data is submitted, the FDA would review the study, summarize it, and have the information revealed thereby added to the drug package insert, a part of the drug's "labeling," for doctors, patients, and payers to peruse.[89] This scheme would thus provide a centralized repository information of potentially high value to the market.[90] In contrast, if no comparative study was performed, the agency would require a labeling notation to that effect as well, putting the relevant audiences on clear notice of this fact (and on alert that a strategic product change might be afoot). While perhaps not a particularly powerful stick, this approach could still add value: under the current regime, prescribers and patients are often left without adequate data to allow them to make informed treatment decisions (e.g., whether to adopt a new version of a drug, switch back from the modified version to the original as a generic, and so on), and payers may likewise be uncertain whether to cover the cheaper off-patent version of the drug, the more expensive patented version, or both.[91]

If this approach proves too mild, more significant interventions to differentiate between companies that attempt to develop clinically valuable drug improvements and those that do not are conceivable. For example, an important regulatory benefit afforded to brand owners is the listing of patents covering the FDA-approved drug in the so-called *Orange Book*.[92] *Orange Book* listings give brands certain advantages during patent litigation and can, effectively, slow down the generics' path to market—even if the patents are ultimately invalidated.[93] This variation of the regulatory solution proposed in this Article, and fully developed in Part IV, would empower the FDA with the discretion to deny *Orange*

[87] *See* Ian Ayres & Amy Kapczynski, *Innovation Sticks: The Limited Case for Penalizing Failures to Innovate*, 82 U. CHI. L. REV. 1781 (2015).
[88] *See infra* Part IV.
[89] *See* 21 C.F.R. § 201.57; *Labeling Information for Drug Products*, U.S. FOOD AND DRUG ADMIN., https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/default.htm (providing general information with respect to what goes on drug labeling on the package insert).
[90] *See infra* Part IV.B.
[91] *See infra* Part III.
[92] *See Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations*, U.S. FOOD AND DRUG ADMIN., https://www.accessdata.fda.gov/scripts/cder/ob/default.cfm (last updated May 2018).
[93] *See* Dogan & Lemley, *supra* note 31, at 710-11.

Book listings to sponsors who fail to provide relevant comparative data to the FDA.[94] More so than clear labeling alone, the stick of denial of an *Orange Book* listing should generate incentives for the sponsors to produce premarket comparative data, and perhaps ultimately lead to drug modifications that are more likely to provide added value for at least some patients.

The rest of the Article proceeds in five parts. Parts I through III set the stage for this Article's proposal for the FDA's novel regulatory authority to induce generation of comparative drug data from pharmaceutical firms, while the proposal itself is laid out in Part IV and further discussed in Part V, which addresses objections. 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 function of patents in incentivizing the development of both pioneering and follow-on drugs, provides relevant background on patent law, and explains why substantive patent law and systemic features of the patent system can result in incomplete analysis of relative drug product quality as a potential proxy for patentability. Part III discusses various forces that interfere with efficient functioning of pharmaceutical markets, enabling strategic product hops driven by secondary patenting.

Focusing on clear labeling, Part IV develops two related approaches for enlisting the FDA's expertise to induce pharmaceutical companies to generate comparative data between closely related versions of drugs that they market. This Part also discusses prior examples of statutory or regulatory schemes in which the FDA engaged in comparative analyses of drugs, sets forth mechanisms for implementing this Article's proposal, and catalogues both immediate and downstream benefits of its adoption. 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 Patent Term Restoration Act, an amendment to the FDCA often referred to simply as the Hatch-Waxman Act,[95] is a statutory scheme for regulating small-molecule drugs in which

[94] *See infra* Part IV.B.
[95] Pub. L. 98-417, § 101, 98 Stat. 1585, 1585-92 (1984).

both the FDA and the PTO play distinct but interrelated roles. The purpose of the Act is to balance incentives for the discovery and development of drugs against the goal of making those medicines available to consumers at reasonable prices.[96] The Act contemplates two types of actors: brand and generic manufacturers.[97] In short, 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 entry of generic equivalents of the branded drugs once the exclusivities expire.[98]

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 by "substantial evidence,"[99] engaging in the back-and-forth with the FDA in order to secure approval,[100] and establishing a market for the drug through extensive promotion and sampling to doctors and patients.[101] The task of the generics is simpler: they must make (or contract to have made) drug products that are essentially the same as those approved by the FDA and marketed by brand companies, while adhering to good manufacturing practices and passing certain tests confirming that what they made is "bioequivalent"

[96] *See* H.R. Rep. No. 98-857, pt. 1, at 14-15 (1984), *reprinted in* 1984 U.S.C.C.A.N. 2647.
[97] *Id.* at 19-20.
[98] *Id.* at 15-17.
[99] 21 U.S.C. § 355(d). *See generally* DANIEL CARPENTER, REPUTATION AND POWER 465-543 (2010).
[100] *See generally New Drug Application (NDA)*, U.S. FOOD AND DRUG ADMIN., 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) (describing the FDA regulatory process).
[101] Chie Hoon Song & Jeung-Whan Han, *Patent cliff and strategic switch: exploring strategic design possibilities in the pharmaceutical industry*, 5 SPRINGERPLUS 692, 699-700 (2016); *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)). On the role of trademark law in the marketing effort, see Gideon Parchomovsky & Peter Siegelman, *Towards an Integrated Theory of Intellectual Property*, 88 VA. L. REV. 1455 (2002). For further discussion of drug marketing and advertising, *see infra* Parts IV.B-C and accompanying text.

to the brand.[102] Crucially, generics need not conduct extensive clinical trials, and can simply rely on the 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 actors typically make with the FDA: brands file New Drug Applications (NDAs), while generics file *Abbreviated* New Drug Applications (ANDAs).[103] 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, NDA sponsors are entitled to certain exclusivities. Under Hatch-Waxman, they receive five years of FDA-enforced exclusivity for any new chemical entity approved to be marketed as a drug,[104] intended largely to serve as a backstop in the circumstances when patents are not available.[105] During this period, which runs five years from the date of NDA approval, the FDA is barred from considering ANDAs on drugs containing the new chemical entity, and generic manufacturers are thereby prevented from relying on the brands' clinical trial data during this time to obtain approval for their copies of the branded drug.[106]

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

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[102] 21 U.S.C. § 355(j); *see also* 21 C.F.R. § 314.127 (2016) (setting forth the prerequisites for ANDA approval); *FDA Ensures Equivalence of Generic Drugs*, U.S. FOOD AND DRUG ADMIN. (Aug. 2002), https://www.fda.gov/drugs/emergencypreparedness/bioterrorismanddrugpreparedness/ucm134444.htm. Brand and generic products, to be sure, need not be exactly chemically equivalent—there is some tolerability in the difference in the generic's composition relative to the brand that would still allow 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 and generic products, such as variations in inactive ingredients, did not bar a finding of bioequivalence). Besides being a requirement for ANDA approval, bioequivalence is critical because, along with pharmaceutical equivalence (e.g., same dosing), it is an essential prerequisite to therapeutic equivalence—and therefore to generic substitution. *See infra* notes 127-128 and accompanying text.

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

[104] *Id.* § 355(j)(5)(F)(ii).

[105] On the significance of these exclusivities, see Rebecca S. Eisenberg, *The Role of the FDA in Innovation Policy*, 13 MICH. TELECOMM. & TECH. L. REV. 345 (2007); 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); Anna B. Laakmann, *A Property Theory of Medical Innovation*, 56 JURIMETRICS J. 117 (2016).

[106] When the underlying patents are challenged by ANDA applicants, that period is shortened to four years. *See* 21 U.S.C. § 355(j)(5)(F)(ii).

process,[107] sponsors may obtain patents covering, for example, chemical compositions embodying the newly invented drugs or new methods of using known chemicals to treat the indicated health conditions. For various reasons,[108] 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. Although the term of one of the patents covering a drug containing a particular active pharmaceutical ingredient can be extended to account for FDA regulatory delays, the extension is capped at five years, and in no event can effective patent life be longer than 14 years from the FDA approval of the NDA.[109]

The Hatch-Waxman Act mandates that sponsors submit information regarding certain patents covering their approved drugs, which the agency then lists in the *Orange Book*.[110] The *Orange Book* embodies a mechanism that provides a critical link between patent and FDA-regulatory aspects of pharmaceuticals.[111] Thus, the Act requires generic manufacturers wishing to market a drug under an ANDA to certify to the FDA that either no relevant patent information was submitted by the sponsor (Paragraph I) or, for each applicable patent, 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).[112]

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 branded drug, which is possible only if the patent claims are invalid or not infringed by the ANDA-approved product. The filing of a Paragraph

[107] As noted above, *see supra* notes 81-83 and accompanying text, there is a statutory provision that authorizes the PTO to request information with respect to drugs from the FDA, *see* 35 U.S.C. § 372(d), but it has not been used very often, *see* Darrow, *supra* note 49, at 402-03. For a proposal to increase interagency cooperation in the healthcare arena beyond the PTO, see Rachel E. Sachs, *Administering Health Innovation*, 39 CARDOZO L. REV. 1991 (2018).

[108] *See infra* Part II.

[109] 35 U.S.C. § 156(g)(6)(A), (c)(3); *see also infra* note 425 and accompanying text (discussing the statutory extension provisions in more detail). The standard patent term is twenty years from effective date of the filing of a patent application. *Id.* § 154(a)(2). On the issue of variation in patent term based on various statutory and non-statutory provisions, see Stephanie Plamondon Bair, *Adjustments, Extensions, Disclaimers, and Continuations: When Do Patent Term Adjustments Make Sense?*, 41 CAP. U. L. REV. 445, 445 (2013).

[110] 21 U.S.C. § 355(b)(1); *see Orange Book*, *supra* note 92.

[111] On the concept of "linkage" between patents and regulatory drug approvals, 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).

[112] 21 U.S.C. § 355(j)(2)(A)(vii)(I)-(IV).

IV certification is deemed by statute to be an act of patent infringement that allows the parties to initiate a lawsuit in order to litigate the issue of the generic's liability,[113] which in turn triggers an automatic 30-month stay against the approval of the ANDA.[114] If the generic obtains a judgment of invalidity or non-infringement of the relevant *Orange Book*-listed patents, it earns permission to market its drug before the patent expiration dates.[115]

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 leads to smaller market shares and, typically,[116] lowered prices of branded drugs, causing significantly reduced profit margins for the sponsor firm.[117] In particular, a judgment invalidating the patent could be financially devastating for the firm unless it has other drugs in the pipeline.[118] A similar result obtains when the patent covering a blockbuster drug expires, a phenomenon sometimes described as the "patent cliff."[119]

Moreover, once the generics enter, the brand's losses are cemented by the generic substitution laws mentioned in the Introduction.[120] Although their 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

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[113] 35 U.S.C. § 271(e)(2)(A).

[114] 21 U.S.C. § 355(j)(5)(B)(iii). To be entitled to the 30-month stay, the brand must file the infringement lawsuit within 45 days of the generic's Paragraph IV notice. *Id.* § 355(b)(3)(C). After 30 months, the FDA will approve the generic, though it might still be kept off the market if the patent litigation is ongoing. In addition, generic firms have the option to challenge patentability of the brand's patents at the PTAB, which generally makes decisions more quickly than the district courts. *See generally* Shepherd, *supra* note 55. At the PTAB, the preponderance of the evidence standard (after a grant of a petition for so-called Inter Partes Review or Post Grant Review) is used to determine whether the challenged claims are unpatentable. 35 U.S.C. § 316(e) (2018). In contrast, issued patents are accorded the presumption of validity in district court litigation, and invalidity therefore must be proven by clear and convincing evidence. *Id.* § 282(a); *see* Microsoft Corp. v. i4i Ltd. P'ship, 564 U.S. 91, 95 (2011). The PTAB, however, has the discretion to deny institution of review of an issued patent for any reason, and that decision is non-appealable. *See* Oil States Energy Servs., LLC v. Greene's Energy Grp., LLC., 138 S. Ct. 1365, 1371 (2018); 35 U.S.C. § 314(d) (2018).

[115] The stay is lifted if the litigation concludes before the 30-month period ends. 21 U.S.C. § (j)(5)(B)(iii)(I)(aa).

[116] Grabowski & Vernon, *supra* note 100.

[117] *See* Song & Han, *supra* note 101.

[118] *See id.*

[119] *Id.*; *see* PHARMTECH.COM, *Responding to the Patent Cliff*, http://www.pharmtech.com/responding-patent-cliff (July 1, 2013). This term can also refer to the phenomenon of a number of blockbuster drug patents expiring simultaneously.

[120] *See supra* note 13 and accompanying text. *See* Kesselheim & Darrow, *supra* note 13.

habit, loyalty,[121] belief that the brand is somehow better,[122] or for some other reason.[123] In many states, substitution laws take a permissive form[124]—in other words, the pharmacist may fill a prescription for a brand with a generic—but in some states the switch is mandatory unless explicitly overridden by doctor's orders.[125] 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.

Nonetheless, generic substitution laws are firmly entrenched, and they reinforce the intuition that prescription drugs operate in a market that is nothing like the market for normal products like liquid hand soap. Indeed, generic substitution laws are motivated in part by some peculiar economics of brand-generic "competition,"[126] and reflect the view that it is unrealistic to expect generic firms to conduct their own advertising given the commodity-like nature of generic drugs and the possibility that other generic entrants might free-ride on the efforts of the one firm that decides to advertise. Although the ultimate result seems harsh on the sponsor, it does reinforce a result contemplated by the Hatch-Waxman scheme—lower drug prices.[127] The idea is that at the expiration of all of the brand's valid exclusivities, the innovator has received all the reward that it was due, and the public can enjoy cost savings from the generics.

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[121] 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).

[122] Given the requirement of therapeutic equivalence for generic substitution, the belief is typically not justified. *See infra* note 128 and accompanying text. *See generally* Livio Garattini & Katelijne van de Vooren, *Safety and Quality of Generic Drugs: A Never Ending Debate Fostered by Economic Interests?*, 13 APPL. HEALTH ECON. HEALTH POL'Y S3 (2015).

[123] *See infra* note 310 and accompanying text (providing examples of studies of patient pressures on prescribers).

[124] *See, e.g.*, CONN. GEN. STAT. ANN. § 20-619 (West 2018) (permitting generic substitution unless the prescriber or purchaser states otherwise).

[125] *See, e.g.*, FLA. STAT. ANN. § 465.025 (West 2018) (mandating generic substitution unless the prescriber states otherwise).

[126] *See generally* Emily Michiko Morris, *The Myth of Generic Pharmaceutical Competition Under the Hatch-Waxman Act*, 22 FORDHAM INTELL. PROP. MEDIA & ENT. L.J. 245 (2012); *see also* Janfei J. Guo & Christina M.L. Kelton, *Competition Between Brand-Name and Generic Drugs* 181, *in* PHARMACEUTICAL PUBLIC POLICY (Thomas R. Fulda, Alan Lyles & Albert I. Wertheimer eds., 2016).

[127] 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).

Significantly, the states tie pharmacists' ability to substitute generics for brands to the FDA's determination that the two are "therapeutic equivalents," which is normally the case for brands and generics.[128] This standard requires, among other things, "identical amounts of the same active drug ingredient in the same dosage form and route of administration."[129] 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.[130] Returning to this Article's central example of extended- versus immediate-release forms of Namenda, the drug modification that led to the *Actavis* antitrust case, one observes that the two are not substitutable because of the difference in dosing. The immediate-release version was indicated for a twice-a-day 10-milligram (mg) dose administration (for a 20 mg total of the active drug a day), while the extended-release version was indicated for one daily 28-mg daily dose,[131] rendering the two therapeutically distinct.[132] The product-hopping strategy discussed 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 patents, then, that this Article now turns.

II. DRUGS, PATENTS, AND PRODUCT CHANGES

A. Primary and Secondary Patents

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

[128] *See Approved Drug Products with Therapeutic Equivalence Evaluations*, *supra* note 110.
[129] *See Orange Book Preface*, U.S. FOOD AND DRUG ADMIN. (38th ed.), https://www.fda.gov/Drugs/DevelopmentApprovalProcess/ucm079068.htm.
[130] *But cf.* Rai & Richman, *supra* note 23 (proposing a way around this rule using so-called suitability petitions at the FDA). Even if the two versions are made substitutable under state law pursuant to the proposals by Professors Rai and Richman, though, the problem that prescribers, patients, and payers lack information about the difference between the two drug versions would remain. In addition, physicians might balk at a rule that allows (or, in some states, even mandates) for their prescriptions to be filled with a drug that, though not proven distinct from the earlier version, has a different dosing profile. Although, to be sure, generic substitutions can always be explicitly overridden by a physician's orders, there may be unknown, unpredictable dangers from substitutions such as those from immediate to extended release tablets that would disfavor making them "automatic" unless specifically contraindicated.
[131] New York *ex rel.* Schneiderman v. Actavis PLC, 787 F.3d 638, 674 (2d Cir. 2015).
[132] *See supra* notes 128-130 and accompanying text (explaining the prerequisites for generic substitution).

patents are the success story of the patent system.[133] Because the pharmaceutical industry is one that requires a high amount of upfront investment, a drug-maker's ability to recoup it by charging supracompetitive prices made possible by patent exclusivity is critical for preserving incentives for pharmaceutical innovation.[134] Indeed, because many drug candidates fail to make it through the FDA approval process, the brand company's ability to "cash in" on those products that do get through and end up being blockbusters can offset the losses associated with drug candidates that are unsuccessful.[135] While the FDA's five-year new chemical entity exclusivity serves as a backstop that provides some reward when no patent can be obtained,[136] by many accounts this period may simply be too short to give pharmaceutical companies sufficient return on investment[137]—especially when the particular drug discovery effort is expected to require significant research and development expenditures.[138]

In many cases, though not all,[139] new drugs represent significant advances in both science and health care. These products are frequently protected by broad patents covering the newly discovered chemical entities[140]—though, to be sure, such patents cannot always be obtained.[141] Generally speaking, though, patents that do cover new active drug ingredients tend to be fairly robust, and their validity is rarely challenged

[133] 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).

[134] Grabowski & Vernon, *supra* note 100.

[135] Joseph A. DiMasi et al., *Innovation in the Pharmaceutical Industry: New Estimates of R&D Costs*, 47 J. HEALTH ECON. 20 (2016).

[136] *See* Held, *supra* note 105.

[137] *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 100; Erika Lietzan, *The Drug Innovation Paradox*, 83 MO. L. REV. 39 (2018).

[138] *See, e.g.*, Henry Grabowski, *Patents, Innovation, and Access to New Pharmaceuticals*, 5 J. INT'L ECON. L. 849, 849–51 (2002); Laura M. McNamee et al., *Timelines of translational science: From technology initiation to FDA approval*, 12 PLOS ONE e0177371 (2017); Erika Lietzan, *The Myths of Data Exclusivity*, 20 LEWIS & CLARK L. REV. 91, 96-101 (2016).

[139] *See, e.g.*, Aidan Hollis, *Me-too drugs: is there a problem?*, http://www.who.int/intellectualproperty/topics/ip/Me-tooDrugs_Hollis1.pdf

[140] *See, e.g.*, C. Scott Hemphill & Bhaven Sampat, *Drug Patents at the Supreme Court*, 339 SCI. 1386, 1386 (2013).

[141] For example, the chemical entity is sometimes known in the art, which relegates the brand owner to less powerful patents, such as those directed to methods of use. 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). One commentator has argued that difficulties of obtaining patent protection for drugs that are similar to those already known have led to diminished innovation incentives in the areas in which innovations useful for human health are likely to be discovered. Benjamin N. Roin, *Unpatentable Drugs and the Standards of Patentability*, 87 TEX. L. REV. 503 (2009).

successfully by generics in Hatch-Waxman litigation.[142] Thus, the principal threat to the exclusivity these patents 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.[143] On the back end, it is of course the expiration of the patent.[144]

Whether, even with the statutory extensions, useful patent 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. Indeed, some recent empirical work has shown that the patent term is probably too short to provide an adquate reward, particularly for certain difficult-to-develop drugs.[145] 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.[146] In addition, and more closely related to this Article's proposal, Professors Gregg Bloche, Neel Sukhatme, and John Marshall suggested that patent term should be tied to the therapeutic value of the underlying drug.[147]

But what about patents on follow-on products, such as extended-release versions of drugs? Consistent with incremental nature of the innovation these products normally embody, brand companies tend to protect them with patents that are narrower than those covering the pioneering versions. This dynamic is captured in the terminology that refers to the patents on the original drug as primary and those on the follow-on as secondary. Secondary patents, sometimes also referred to as "improvement patents,"[148] tend to be weaker than primary patents, and

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[142] *See* Hemphill & Sampat, *supra* note 54.

[143] Shamnad Basheer, *The Invention of an Investment Incentive for Pharmaceutical Innovation*, 15 J. WORLD INTELL. PROP. (2012); Lietzan, *supra* note 137; Song & Han, *supra* note 101.

[144] Song & Han, *supra* note 101, at 692.

[145] Budish et al., *supra* note 137.

[146] Basheer, *supra* note 143; Budish et al., *supra* note 137; Lietzan, *supra* note 137; Benjamin N. Roin, *The Case for Tailoring Patent Awards Based on the Time-to-Market of Inventions*, 61 UCLA L. REV. 672 (2014); 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.

[147] Gregg Bloche et al., *Health Policy's Gordian Knot: Rethinking Cost Control*, HEALTH AFF. BLOG (Apr. 26, 2017), https://www.healthaffairs.org/do/10.1377/hblog20170426.059805/full.

[148] *See, e.g.*, Hughes Aircraft Co. v United States, 717 F.2d 1351, 1362 (Fed. Cir. 1983) (contrasting patents on "pioneer inventions" with "improvement patents"); *see also In re* Braat, 937 F.2d 589, 593 (Fed. Cir. 1991) (discussing "improvement patents" in the context of the

empirical research shows that they are invalidated more frequently in litigation.[149] Moreover, because these patents by definition cover a variation of an already-approved drug, the approval of the underlying product generally does not take up nearly as much research and development time (and cost) as that of the pioneering version.[150] 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" or the nature of the innovation,[151] even if those attributes could be somehow quantifiable, secondary pharmaceutical patents get the term of twenty years from the effective date of the application just as all others.[152] Also, just as primary patents, these patents are listed in the *Orange Book* (as covering the follow-on drug) and receive associated FDA-administered benefits, including the requirement of a Paragraph IV certification if the generic wishes to market the new product before patent expiration and, normally, a 30-month stay after the litigation commences.[153]

To be sure, the very division of patents into primary and secondary categories is somewhat arbitrary—a patent is a patent, and it

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obviousness-type double patenting doctrine). On the concept of pioneer patents generally, see Brian J. Love, *Interring the Pioneer Invention Doctrine*, 90 N.C. L. REV. 379 (2011).

[149] *See* Hemphill & Sampat, *supra* note 54. *But see* 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) (contending that many secondary patents embody valuable pharmaceutical inventions).

[150] *See* Himanshu Gupta et al., *Patent Protection Strategies*, 2 J. PHARM. BIOALLIED SCI. 2 (2010); *see also* John F. Duffy, *A Timing Approach to Patentability*, 12 LEWIS & CLARK L. REV. 343, 366 (2008) (contending that "the grant of improvement patents to a pioneer patentee may present issues different from the canonical situation in which many similarly situated inventors are seeking patents conferring immediate market exclusivity").

[151] *See* Robert P. Merges & Richard R. Nelson, *On the Complex Economics of Patent Scope*, 90 COLUM. L. REV. 839, 868-84 (1990) (questioning whether this established feature of patent law always serves the purposes of innovation policy); *see also* THOMAS, *supra* note 67, at 8 (explaining that "statutory standards [of patentability] are applied neutrally to each kind of invention, whether it may be characterized as an 'original' (such as a medication that has never been previously approved by the FDA) or an 'improvement' (such as a new formulation of a known medication)").

[152] 35 U.S.C. § 154(a)(2). Such patents, to be sure, do not qualify for regulatory delay extensions under § 156. *See also infra* note 425 and accompanying text (using this feature of the statute as an example of "discrimination" between different patent types).

[153] *See supra* notes 113-114 and accompanying text. However, if the patent issues and is asserted after the ANDA has been approved, then a 30-month stay is not granted. *See* 35 U.S.C. § 271(e)(2)(A) (covering only ANDAs submitted "for a drug claimed in a patent or the use of which is claimed in a patent"); *cf.* Endo Pharm. Inc. v. Amneal Pharm., LLC, Nos. 12-cv-8115 (TPG), *et al.*, 2016 WL 1732751, at *3-4 (S.D.N.Y. Apr. 29, 2016)) (explaining the significance of the effective date of the ANDA relative to the date of patent issuance in Hatch-Waxman proceedings for purposes of relief under § 271(e)(4)), *aff'd on other grounds sub nom.* Endo Pharm. Inc. v. Teva Pharm. USA, Inc., 731 F. App'x 962, 967 n.4 (Fed. Cir.) (nonprecedential), *vacated in part on other grounds*, 729 F. App'x 936 (Fed. Cir. 2018).

does not issue from the PTO with an ordinal label.[154] In the pharmaceutical space, though, a clear pattern of patenting has emerged that makes the distinction appropriate as a heuristic matter.[155] A broad patent, often containing claims to a group of chemical compounds that includes the active ingredient of the drug, is followed some years later by new claims directed to the active ingredient mixed with so-called polymeric carriers, tablets containing the active ingredient that have certain dissolution rates, specific crystalline forms of the active ingredient, and the like.[156] Although such claims can face an uphill battle at the PTO, brand companies devote significant resources to their prosecution and often overcome the initial rounds of rejections from patent examiners to obtain allowance. The issuance of the new patents is, in turn, sometimes accompanied by a strategic 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,[157] Dr. Kessler expressed concerns about the practice in the 1990s.[158]

For a concrete example of the primary-secondary patent dynamic, though one that could not be fairly characterized as a strategic product hop because the modification resulted in a provably better product,[159] 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."[160] This claim was the representative claim at issue in *AstraZeneca AB v. Anchen Pharmaceuticals*, a case to which I will return in the next Section.[161] The

[154] *See generally* Christopher M. Holman et al., *Patentability Standards for Follow-on Pharmaceutical Innovation*, 37 BIOTECH. L. REP. 131 (2018). *But cf.* Dmitry Karshtedt, *The Completeness Requirement in Patent Law*, 56 B.C. L. REV. 949 (2015) (proposing a limited patent right for a particular set of inventions).

[155] *See* Hemphill & Sampat, *supra* note 140. The FDA, too, implicitly recognizes the difference between "primary" and "secondary" products via NDA classification codes. *See infra* notes 434-435 and accompanying text.

[156] *See generally* 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 (2010).

[157] HOVENKAMP ET AL., *supra* note 7.

[158] Kessler, *supra* note 71, at 347 ("[W]hat seems to be driving many corporate decisions to develop [extended release forms of drugs], however, is not convenience or compliance, but economics.)".

[159] *See infra* notes 178-181 & 216-222 and accompanying text (discussing the advantages of Seroquel XR over IR).

[160] U.S. Pat. No. 5,948,437, claim 1 (filed May 28, 1997).

[161] *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 F. App'x 999 (Fed. Cir. 2013) (mem.).

phrase of particular note in this claim is "a gelling agent," the addition of which constitutes one of the reasons that the claim is patentable.[162] 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.[163] In contrast, the corresponding primary patent was significantly broader: it covered 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 immediate-release quetiapine.[164]

In patent terminology, the two patents have a "genus-species" relationship,[165] whereby the subject matter claimed in the narrower, secondary "gelling agent" patent is a "species" of the various embodiments covered 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 patent belonging to the sponsor. Therefore, third parties are prevented form marketing *either* the extended-release version *or* the immediate-release version of the quetiapine drug during the life of the first patent,[166] but they can market the immediate-release version—though not the extended-release version,[167] unless the second patent is invalidated or adjudged non-infringed—after the first patent

[162] *See* U.S. Pat. No. 4,879,288 (filed Mar. 20, 1987).
[163] *AstraZeneca*, 2012 WL 1065458, at *2-8.
[164] *See id.* at *55.
[165] *See, e.g.*, Dmitry Karshtedt, *Limits on Hard-to-Reproduce Inventions: Process Elements and Biotechnology's Compliance with the Enablement Requirement*, 3 HASTINGS SCI. & TECH. L.J. 109, 128-33 (2011) (describing genus-species dynamics in pharmaceutical patent claims).
[166] *See* Merges & Nelson, *supra* note 151, at 860-68 (discussing the concept of so-called "blocking" patents). *See generally* Douglas L. Rogers, *Double Patenting: Follow-on Pharmaceutical Patents that Suppress Competition*, 14 NW. J. TECH. & INTELL. PROP. 317 (2017) (questioning the policy of allowing such patents).
[167] To be sure, a generic is sometimes able to "design around" the secondary patent and make a product that is bioequivalent to the brand (and ultimately substitutable), but not infringing. *See generally* Freilich, *supra* note 102; *see also* Holman et al., *supra* note 154, at 137. Nonetheless, given the stringent requirements for therapeutic equivalence, such a strategy is often unsuccessful unless the brand's secondary claims are badly drafted—and even then, the patentee might still succeed proving infringement under the doctrine of equivalents. *See, e.g.*, Intendis GmbH v. Glenmark Pharm. Inc., USA, 822 F.3d 1355 (Fed. Cir. 2016). Still another possible way out for a follow-on researcher is the filing of a special NDA under a § 505(b)(2) application, which is something of a hybrid between an ANDA and an NDA (it can, for example, allow applicants to seek approval of a drug with a strength different from that of the original drug with less clinical trial information than full ANDA). *See* 21 U.S.C. § 355(b)(2). Nonetheless, a well-drafted patent claim combined with a product-hopping strategy can limit the marketing of drugs approved under § 505(b)(2) in the same way that it can limit the marketing of drugs under ANDAs. *See* Chelsea E. Ott, Comment, *The Evolution of Pharmaceutical Regulatory Gaming Practices*, 47 SETON HALL L. REV. 849, 851 (2017); *see also supra* note 102 and accompanying text.

expires.

This story is complicated somewhat by a subsection of the Patent Act that relieves firms from infringement liability for research "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,"[168] such as compliance with the FDCA required to receive FDA approval.[169] This provision, by its terms, can cover research designed to obtain approval of a new (and perhaps improved) version of the branded pioneering drug by a company other than that drug's sponsor. Although this research exemption does not permit a competitor to actually market a drug product covered by someone else's patent,[170] the competitor is nonetheless allowed to obtain its own secondary patents[171] and use them to support the marketing of the reformulated product when the primary patents expire[172]—as long as the sponsor of the original drug does not also acquire secondary patents covering that particular modification.

Typically, however, the original drug's sponsor will control both the pioneering drug and its improvements along with the corresponding patents.[173] Putting to one side the role of the dominant patent, this state of affairs likely stems from the fact that the discoverer of the new active chemical ingredient underlying the drug normally has an immense head start over others with respect to various facets of that chemical. In particular, the sponsor is often in possession of a great deal of know-how

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[168] 35 U.S.C. § 271(e)(1).

[169] Merck KGaA v. Integra Lifesciences I, Ltd., 545 U.S. 193, 202 (2005); Classen Immunotherapies, Inc. v. Biogen IDEC, 659 F.3d 1057, 1072 (Fed. Cir. 2011) (explaining that the "statutory purpose" of § 271(e)(1) is "to facilitate market entry upon patent expiration").

[170] *See* Momenta Pharm., Inc. v. Teva Pharm. USA Inc., 809 F.3d 610 (Fed. Cir. 2015).

[171] *See* Classen Immunotherapies, Inc. v. Elan Pharm., 786 F.3d 892, 898 (Fed. Cir. 2015) ("Filing a patent application is generally not an infringement of a patent. It is not the making, using, offering to sell, selling, or importing of an invention.").

[172] *But cf.* Acorda Therapeutics, Inc. v. Roxane Labs., Inc., Nos. 17-2078, 17-2134, 2018 WL 4288982, at *19 (Fed. Cir. Sept. 10, 2018) ("[S]uch a potential innovator might or might not be willing to research in the blocked space without a license to a blocking patent—even if the research itself is within the safe harbor provided by 35 U.S.C. § 271(e)(1)—and wait until it has already developed and patented its aimed-at improvement to negotiate for a cross-license with the blocking patent's owner to share the profits from the improvement.); *see also id.* at *21.

[173] *See, e.g.*, 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"). Professor Jonathan Darrow has written about a significant exception. 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); *see also infra* 436-440 and accompanying text (discussing enantiomers); *cf. Acorda*, 2018 WL 4288982, at *21 n.18 (accepting this intuition).

and data that remains undisclosed even as the relevant patent applications and other descriptions of the product, such as those in scientific articles, become public.[174] Accordingly, potential competitors face formidable obstacles in developing modifications that would threaten the original sponsor's market position with respect to follow-on products.[175] This Article's proposal does not concern the scenario in which a competitor develops the modification[176]—by definition, this cannot be a product hop. Thus, the examples discussed in the Article, including Asacol, Namenda, and Seroquel, all involve the more typical set of facts in which the pioneer and the follow-on are marketed by the same firm or by closely related entities, such as wholly-owned subsidiaries.[177]

In the case of Seroquel, immediate-release quetiapine was a novel drug type that turned out to be particularly effective for bipolar depression, as well as for other conditions like schizophrenia and psychosis.[178] The version with the gelling agent, as the claim indicates, is the "sustained release" form of quetiapine.[179] The extended-release patent from which the representative claim above is drawn expired in 2017, while the pioneering patent on quetiapine expired in 2012.[180] The courts have upheld the validity of the secondary, Seroquel XR patent based in

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[174] *See* W. Nicholson Price II, *Expired Patents, Trade Secrets, and Stymied Competition*, 92 NOTRE DAME L. REV. 1611, 1620-32 (2017) (discussing this dynamic and explaining why it is particularly salient in the pharmaceutical industry); *see also* W. Nicholson Price II, *Regulating Secrecy*, 91 WASH. L. REV. 1769, 1799-1802 (2016); W. Nicholson Price II & Arti K. Rai, *Manufacturing Barriers to Biologics Competition and Innovation*, 101 IOWA L. REV. 1023 (2016) (discussing a similar dynamic with so-called "biologic" drugs).

[175] *See also infra* Part IV.B (explaining the impact of this feature of the market on advertising).

[176] For another recent (counter-)example of sorts, see Otsuka Pharm. Co. v. Price, 869 F.3d 987 (D.C. Cir. 2017) (describing a case in which another firm developed an alternative version of a drug in spite the regulatory-exclusivity protection in place for the brand).

[177] As to the question of the standard for determining when the firm is sufficiently related to the prior sponsor of a product for the "same firm" regime to apply, the FDA has faced a similar issue in the interpretation the "same sponsor" provision in the Biologics Price Competition and Innovation Act. *See* 42 U.S.C. § 262(k); *see also* BIOTECHNOLOGY INDUSTRY ORGANIZATION, Comment on *Draft Guidance for Industry: Reference Product Exclusivity for Biological Products Filed Under Section 351(a) of the PHS Act* at 13 (Docket No. FDA-2013-D-1165, 79 Fed. Reg. 45448 (August 5, 2014)) (analyzing this provision); *infra* notes 479-480 and accompanying text. This issue should be resolvable under general corporate law principles. For example, one of the firms involved in the marketing of the new version of Namenda, Actavis, now owns the firm that marketed the prior version, Forest, as a wholly owned subsidiary. Such a relationship should be sufficiently close for the owner of the new version of the drug to qualify as the "same sponsor."

[178] *See* Michael E. Thase, *Quetiapine Monotherapy for Bipolar Depression*, 4 NEUROPSYCHIATRIC DISEASE TREATMENT 11, 12-13 (2008).

[179] *See Approval Package for Application*, NDA 22-047, U.S. FOOD AND DRUG ADMIN., CTR. FOR DRUG EVALUATION AND RES. (May 17, 2007), https://www.accessdata.fda.gov/drugsatfda_docs/nda/2007/022047Orig1s000Approv.pdf.

[180] *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, at *4, *55 (D.N.J. Mar. 29, 2012), *aff'd*, 498 F. App'x 999 (Fed. Cir. 2013) (mem.).

part on evidence that the switch from IR to XR has led to certain therapeutic improvements.[181] To understand the relevance of such information on patentability—and to draw a further connection between secondary patents and the product-hopping phenomenon—some background on specific aspects of substantive patent law is in order.

B. Pharmaceutical Patenting and Product Changes

1. The sponsor's non-obviousness challenge and "unexpected results"

Before returning to the substantive provision of the Patent Act of principal relevance to secondary patents, it is useful to briefly review patent prosecution procedures. To obtain patent rights, inventors—or, more commonly, the firms those inventors work for—begin by filing patent applications with the PTO. An application contains one or more claims, such as the illustrative "gelling agent plus quetiapine" claim above, desired by the applicants. A patent examiner assesses the claims for compliance with the various requirements of patentability, typically a time-consuming process that involves multiple iterations of arguments between the applicant and the examiner. 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 brand can use it to keep generics out until invalidation (or adjudication of non-infringement), a determination of unpatentability in a PTO post-issuance review, or expiration.[182]

Of the various requirements of patentability, the one that is usually the most difficult to overcome for the drug sponsor seeking to obtain a secondary patent is the non-obviousness requirement, codified in 35 U.S.C. § 103. While the novelty requirement of § 102 prohibits patents on subject matter that has become part of the public domain, the non-obviousness requirement of § 103 essentially bars patents on claims that, although not identically disclosed by prior publications or activities, are so close to what is already known[183]—the universe of disclosures sometimes collectively described as "the prior art"—as to be within the public's grasp.[184] This section states:

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[181] *See generally id.* For a comparative study in the academic literature, 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. PSYCHOPHARMACOLOGY 217 (2012).
[182] *See supra* notes 112-119 and accompanying text.
[183] *See* 35 U.S.C. §§ 102, 103.
[184] Bonito Boats, Inc. v. Thunder Craft Boats, Inc., 489 U.S. 141, 156 (1989).

> 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.[185]

Because the term "obvious" is not self-defining, the structure of the § 103 inquiry had to be developed by courts. Three of the four 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."[186] The ultimate question is whether, given the differences, the fictitious "person of ordinary skill in the art" would readily bridge them.[187] Further glosses by the United States Court of Appeals for the Federal Circuit, the court with exclusive jurisdiction over patent appeals, have established that those challenging claims on obviousness grounds must typically show some motivation to combine or modify the relevant prior art to make the claimed invention,[188] and also demonstrate that the inventor would have had a reasonable expectation of success involving the patented subject matter at the time the application was filed.[189]

In addition, as the fourth factor, courts in the non-obviousness inquiry consider "[s]uch secondary considerations as commercial success, long felt but unsolved needs, failure of others"[190] and others (e.g., industry praise and licensing),[191] sometimes also called "objective indicia of non-obviousness."[192] Because, at the time when a patent application is pending before the PTO, a commercial product might not yet exist, such evidence generally plays a bigger role during litigation as

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[185] 35 U.S.C. § 103(a).
[186] 383 U.S. 1, 17-18 (1966).
[187] *See id.*
[188] *See* Arctic Cat Inc. v. Bombardier Recreational Prods. Inc., 876 F.3d 1350, 1359-60 (Fed. Cir. 2017); *see also* KSR Int'l Co. v. Teleflex Co., 550 U.S. 398 (2007).
[189] *See In re* Stepan Co., 868 F.3d 1342, 1345-46 (Fed. Cir. 2017).
[190] *Graham*, 383 U.S. at 18. *See generally* Jonathan J. Darrow, *Secondary Considerations: A Structured Framework for Patent Analysis*, 74 ALB. L. REV. 47 (2011)
[191] *See* Natalie A. Thomas, Note, *Secondary Considerations in Nonobviousness Analysis: The Use of Objective Indicia Following* KSR v. Teleflex, 86 N.Y.U. L. REV. 2070, 2076 n.31 (2011).
[192] *In re* Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig., 676 F.3d 1063 (Fed. Cir. 2012); Stratoflex, Inc. v. Aeroquip Corp., 713 F.2d 1530, 1538-39 (Fed. Cir. 1983).

opposed to prosecution.[193] In the Seroquel case, for example, proof of Seroquel XR's commercial success and the long-felt need for effective treatments of bipolar depression were significant factors in convincing the trial court to uphold the validity of the XR patent.[194] Secondary considerations can generally only help the patentee,[195] though establishing their relevance for a claim's non-obviousness does require a showing of some connection between the evidence and the patented invention.[196] For example, if the commercial success of the claimed invention's embodiment is attributable mainly to marketing 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.[197]

The admissibility of secondary considerations, which reflect the experiences of pharmaceutical market participants, is somewhat in tension with the oft-stated principle that patent law is not concerned with the creation of inventions that work better than those already on the market.[198] In particular, case law interpreting the utility requirement of patentability, codified in § 101, includes forceful statements like "[a]ll that the law requires is, that the invention should not be frivolous or injurious to the well-being, good policy, or sound morals of society. . . . If it be not extensively useful, it will silently sink into contempt and disregard."[199] When it comes to the non-obviousness requirement, though, while some decisions hold that the case against patentability encapsulated by the first three *Graham* factors can overwhelm secondary considerations,[200] the latter can still make a significant difference in

[193] *See* Reilly, *supra* note 50, at 577.

[194] 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, at *48-55 (D.N.J. Mar. 29, 2012), *aff'd*, 498 F. App'x 999 (Fed. Cir. 2013) (mem.).

[195] The one secondary consideration that can help the patent challenger is near-simultaneous invention of the claim's subject matter by multiple inventors. *See, e.g.*, *In re* Merck & Co., 800 F. 2d 1091, 1098 & n.11 (Fed. Cir. 1986).

[196] *See* ClassCo, Inc. v. Apple, Inc., 838 F.3d 1214, 1220 (Fed. Cir. 2016).

[197] *See, e.g.*, *In re* Mageli, 470 F.2d 1380, 1384 (C.C.P.A. 1973); *see* Robert P. Merges, *Commercial Success and Patent Standards: Economic Perspectives on Innovation*, 76 CALIF. L. REV. 805, 860 (1988); *see also* Geo. M. Martin Co. v. Alliance Mach. Sys. Int'l LLC, 618 F.3d 1294, 1305 (Fed. Cir. 2010) ("Industry praise must also be linked to the patented invention.").

[198] *See generally* Price, *supra* note 43; *see also* Carrier & Shadowen, *supra* note 7, at 181 ("The granting of a patent by the U.S. Patent and Trademark Office (PTO) certainly does not guarantee, or even suggest, that the reformulated product is superior in any way to existing products.").

[199] *See* Lowell v. Lewis, 15 F. Cas. 1018, 1019 (C.C.D. Mass. 1817) (No. 8568) (Story, Circuit Justice); *see also* MERGES & DUFFY, *supra* note 43, at 201. For a proposal for a re-invigorated "commercial utility" requirement, see Michael Risch, *Reinventing Usefulness*, 2010 BYU L. REV. 1195, 1240-41. *But cf.* Sean B. Seymore, *Making Patents Useful*, 98 MINN. L. REV. 1046 (2014) (contending that the utility requirement, as currently enforced, has been applied in a highly subjective manner and should be eliminated).

[200] *See, e.g.*, Pfizer, Inc. v. Apotex, Inc., 480 F.3d 1348, 1372 (Fed. Cir. 2007) ("Although secondary considerations must be taken into account, they do not necessarily control the

bolstering the patentee's case.[201] Thus, proponents of patentability often introduce real-world data, which are often purported to speak to the objective qualities of the claimed invention in contradistinction to what came before,[202] in order to develop secondary considerations in litigation or prosecution.

Another way such data can come in is under the doctrine of unexpected results, which is of particular significance to this Article's proposal for eliciting comparative drug information.[203] This doctrine, which occupies the murky space in the law of § 103 between the first three *Graham* factors and secondary considerations,[204] holds that the case

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obviousness conclusion."); Cubist Pharm., Inc. v. Hospira, Inc., 805 F.3d 1112, 1126 (Fed. Cir. 2015) (similar); *see also* Am. Innotek, Inc. v. United States, 706 F. App'x 686, 686 (Fed. Cir. 2017) (nonprecedential) (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).

[201] *See, e.g.*, Plantronics, Inc. v. Aliph, Inc., 724 F.3d 1343, 1357 (Fed. Cir. 2013) ("Because evidence pertaining to objective considerations raises genuine issues of material fact, the district court's decision [to grant summary judgment that the asserted claims would have been obvious] is reversed as to all the asserted claims in this case.").

[202] *Apple*, 839 F.3d at 1048-49, 1052-57; Ormco Corp. v. Align Tech., Inc., 463 F.3d 1299, 1311-12 (Fed. Cir. 2006) ("[I]f the feature that creates the commercial success was known in the prior art, the success is not pertinent."); *see also* Sanofi-Aventis Deutschland GmbH v. Glenmark Pharm. Inc., USA, 748 F.3d 1354, 1360-61 (Fed. Cir. 2014).

[203] *See, e.g.*, Prometheus Labs., Inc. v Roxane Labs., Inc., 805 F.3d 1092, 1098 (Fed. Cir. 2015) ("The genus-species distinction may have particular relevance in the field of personalized medicine, where, for example, a particular treatment may be effective with respect to one subset of patients and ineffective (and even harmful) to another subset of patients. Singling out a particular subset of patients for treatment (for example, patients with a particular gene) may reflect a new and useful invention that is patent eligible despite the existence of prior art or a prior art patent disclosing the treatment method to patients generally. An obviousness rejection likely would not be appropriate where the new patient subset displayed unexpected results.") (citation omitted); s*ee also* Sanofi v. Watson Labs., Inc., 875 F.3d 636, 647-50 (Fed. Cir. 2017) (upholding non-obviousness of patent claims based on the lack of a reasonable expectation of success of the drug in the claimed populations.).

[204] *See Sanofi-Aventis*, 748 F.3d at 1360-61 (appearing to treat unexpected results as part of the motivation inquiry); *see also* Hoffman-La Roche Inc. v. Apotex Inc., 748 F.3d 1326, 1334 (Fed. Cir. 2014) (discussing unexpected results without mentioning "secondary considerations" or "objective indicia"); Aventis Pharma Deutschland GmbH v. Lupin, Ltd., 499 F.3d 1293, 1301-03 (Fed. Cir. 2007) (similar); *cf. In re* Papesch, 315 F.2d 381, 391 (C.C.P.A. 1963) ("[A] compound and all of its properties are inseparable."). *But see* Bristol-Myers Squibb Co. v. Teva Pharm. USA, Inc., 752 F.3d 967, 976-77 (Fed. Cir.) (calling unexpected results "a secondary consideration"), *reh'g en banc denied*, 769 F.3d 1339 (Fed. Cir. 2014) (mem.); Transocean Offshore Deepwater, Inc. v. Maersk Drilling USA, Inc., 699 F.3d 1340, 1351-52 (Fed. Cir. 2012) (similar); *Pfizer*, 480 F.3d at 1372 (similar); *see also* Millennium Pharm., Inc. v. Sandoz, Inc., 862 F.3d 1356, 1363, 1367-68 (Fed. Cir. 2017). *Cf.* Frederick G. Vogt, Comment, *Unexpected Results: The Current Status of Obviousness Determinations for Pharmaceutical and Biotechnology Patents*, 29 TEMP. J. SCI. TECH. & ENVTL. L. 305, 310 (2010) ("Judge Rader noted that unexpected results serve as 'independent evidence of nonobviousness,' going beyond just a secondary or confirmatory consideration.") (quoting Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc., 520 F.3d 1358, 1365 (Fed. Cir. 2008)); *but see id.* at 308 (noting that unexpected results have been described as "secondary considerations"); *see also* Thomas, *supra* note 191, at 2095. It is notable that a Federal

for patentability is strengthened when "the claimed invention exhibits some superior property or advantage that a person of ordinary skill in the relevant art would have found surprising or unexpected."[205] Such evidence, presumably,[206] can counter a claim that an ordinary artisan would have had a reasonable expectation of success in developing a particular drug modification, such as an extended-release formulation.[207]

Circuit judge sitting by designation in a high-profile district court case revolving around non-obviousness refused to address whether unexpected results are a part of the inquiry under first three *Graham* factors or the fourth, suggesting that the issue is unsettled. *See* Allergan, Inc. v. Teva Pharm. USA, Inc., No. 2:15-cv-1455-WCB, 2017 WL 4803941, at *47 n.37 (E.D. Tex. Oct. 16, 2017) ("Allergan characterizes 'unexpected results' as a secondary consideration. In the Court's view, however, in a case such as this one that factor is more appropriately viewed not as a secondary consideration, but as part of the initial stage of the obviousness analysis. For that reason, the Court has analyzed the unexpected results argument in part I.A., rather than as one of the objective considerations discussed in part I.B. . . . [R]egardless of how the unexpected results issue is characterized, the Court has considered the evidence on that issue, as well as the evidence of the (other) objective indicia of nonobviousness, together with all of the other evidence pertaining to the obviousness inquiry, as the Federal Circuit has instructed."), *appeal docketed*, No. 18-1130 (Fed. Cir. Nov. 1, 2017); *see also Bristol-Myers Squibb*, 769 F.3d at 1352-1359 (Taranto, J., dissenting from denial of rehearing en banc) (pointing out tensions in the Federal Circuit's approaches to the doctrine of unexpected results and other aspects of the non-obviousness inquiry and calling for en banc action to resolve them).

[205] *In re* Soni, 54 F.3d 746, 750 (Fed. Cir. 1995). *But cf.* Custom Accessories, Inc. v. Jeffrey-Allan Indus., Inc., 807 F.2d 955, 960 n.12 (Fed. Cir. 1986) ("Finding that an invention is an 'improvement' is not a prerequisite to patentability. It is possible for an invention to be less effective than existing devices but nevertheless meet the statutory criteria for patentability.").

[206] *But cf.* Laura G. Pedraza-Fariña, *Patent Law and the Sociology of Innovation*, 2013 WIS. L. REV. 813, 851-54, 870-72 (questioning the evidentiary value of unexpected results discovered after filing as irrelevant to the question of motivation in the non-obviousness inquiry); *see id.* at 854 ("[T]he fact that one of these enantiomers was unexpectedly found to have none of the toxic effects with all the therapeutic effects—while unexpected—would likely have been noticed by any independent scientist pursuing this research program. In addition, the low likelihood of finding one enantiomer with all the therapeutic benefits and none of the toxic effects did not ex ante discourage the line of research that would attempt separation of the enantiomers. In other words, the label 'unexpected results' in this case does not serve as a proxy for identifying a risky line of research that requires patent inducement."); *see also* Mark A. Lemley, *Expecting the Unexpected*, 92 NOTRE DAME L. REV. 1369 (2017) (maintaining that, when ex-post discovered unexpected results conflict with the conclusion that the claimed invention would have been obvious to try, the former should give way and the claims should be held obvious). *See generally* Douglas L. Rogers, *Obvious Confusion Over Properties Discovered After a Patent Application*, 43 AIPLA Q.J. 489 (2015) (exploring this problem in depth). The Federal Circuit currently accepts ex-post discovered unexpected results to show non-obviousness. *See, e.g.*, *Sanofi-Aventis*, 748 F.3d at 1360-61; *see also Bristol-Myers Squibb*, 769 F.3d at 1340-41 (Dyk, J., concurring in denial of rehearing en banc) (arguing for a contrary rule). One treatise has usefully explained the dual evidentiary function of unexpected results. DONALD S. CHISUM ET AL., INTELLECTUAL PROPERTY LAW 77 (3d ed. 2015) ("The relevance of evidence of comparative utility is in part direct and in part inferential. It is direct that the new function is part of the inventive concept, the 'subject matter as a whole,' which must be obvious under Section 103. It is inferential in the sense that the prior art's failure to reveal the claimed invention despite its advantageous qualities tends to confirm that it was unexpected and unobvious. It would be contrary to normal economic incentives for obvious, advantageous subject matter to remain dormant.").

[207] *See, e.g.*, *Millennium Pharm.*, 862 F.3d at 1369 ("[W]e conclude that the district court clearly erred in finding that a person of ordinary skill would obviously make the D-mannitol ester in order

According to one commentator, unexpected results are "the most prevalent form of evidence of non-obviousness relied on by patent applicants during patent examination."[208] In one case, though affirming the PTO's rejection of a claim on a modification of a prior art chemical compound as obvious, the United States Court of Customs and Patent Appeals[209] explained:

> When considering that minor advances in activity are eagerly sought in pharmaceutical chemistry, a showing of nine and six times more activity than the most active compound of the art is indeed most significant, representing a different order of magnitude, and is proof of unobviousness and unexpected beneficial properties in a new compound.[210]

Notably, a showing of unexpected results must be made in a comparison with the "closest single prior art reference."[211] In a typical secondary-patent case raising the possibility of product hopping, the closest prior art against the desired claims will often constitute the patentee's own disclosures related to the subject matter of the primary patent, if not the primary patent itself.[212] Intimate familiarity with the

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to solve the problem of providing an effective form of bortezomib. The unexpected properties of an unexpectedly produced new compound, and the ensuing pharmaceutical efficacy and benefit, negate the district court's ruling of obviousness.").

[208] Harris A. Pitlick, *Some Thoughts About Unexpected Results Jurisprudence*, 86 J. PAT. & TRADEMARK OFF. SOC'Y 169, 169 (2004). Thus, while the Patent Act does not require superiority of the claimed invention to prior products for patentability, Ryco, Inc., v. Ag-Bag Corp., 857 F.2d 1418, 1424 (Fed. Cir. 1988), in practice the evidence of an unexpectedly improved product can be critical in overcoming the § 103 hurdle. This evidence is likely to be especially salient in secondary-patent cases, when there may be a strong case for motivation to make the claimed formulation that could be potentially overcome with unexpected results. *See, e.g.*, Prometheus Labs., Inc. v Roxane Labs., Inc., 805 F.3d 1092, 1098 (Fed. Cir. 2015); Senju Pharm. Co., v. Lupin Ltd., 780 F.3d 1337, 1351-53 (Fed. Cir. 2015); *Hoffman-La Roche*, 748 F.3d at 1334. *See generally* Vogt, *supra* note 204 (providing several other examples).

[209] Decisions of the Court of Customs and Patent Appeals are binding precedent on the Federal Circuit. *See* South Corp. v. United States, 690 F.2d 1368, 1369 (Fed. Cir. 1982) (en banc).

[210] *In re* Carabateas, 345 F.2d 1013, 1017 (C.C.P.A. 1965). Interestingly, the court also noted: "When a new compound so closely related to a prior art compound as to be structurally obvious is sought to be patented based on the alleged greater effectiveness of the new compound for the same purpose as the old compound, clear and convincing evidence of substantially greater effectiveness is needed." *Id.* The court held that, while such evidence was present in the record, it was overcome by evidence of increased analgesic activity of other prior art compounds that have undergone a similar modification to the compounds claimed by the applicant. *Id*. at 1018; *see also In re* May, 574 F.2d 1082, 1092-95 (C.C.P.A. 1978) (concluding that unexpected non-addictive properties of an analgesic render the claims non-obvious). To be sure, a claim of unexpected results does not always relate to comparative *clinical* utility. For a discussion of unexpected results based on increased chemical stability and other manufacturing-type improvements, *see infra* notes 442-444 and accompanying text.

[211] *In re* Merchant, 575 F.2d 865, 868 (C.C.P.A. 1978).

[212] *See generally* Rogers, *supra* note 166.

prior art that it must overcome in order to obtain the secondary patent, and the concomitant ability to shape the presentation of any relevant comparative information,[213] likely gives the sponsor a significant leg up in the process[214]—and may yet be another reason that competition for the development of follow-on drug versions is rarely observed.[215] The challenge of overcoming one's own prior art was, indeed, the general setting for both Seroquel and Namenda extended-release patents, but there are important contrasts between the two sets of product changes in terms what data was introduced before the decision-maker in order to develop unexpected results.

In the Seroquel case, *AstraZeneca AB v. Anchen Pharmaceuticals*, the district court began the analysis of the validity of the XR claims under § 103 by determining that the defendants put on fairly weak evidence of motivation to make the claimed "gelling agent" formulation.[216] Furthermore, it noted that there were general doubts in the literature that extended-release versions of psychiatric drugs like Seroquel would be safe and effective.[217] Thus, AstraZeneca started off with a strong case against obviousness, but the unexpected results helped it further. The court found, based on the testimony of experts, that "Seroquel XR has a sedation profile that is unexpectedly superior as compared to the sedation of Seroquel IR" and "is better tolerated than Seroquel IR in the treatment of bipolar depression."[218] The court

[213] *Cf.* Daralyn J. Durie & Mark A. Lemley, *A Realistic Approach to the Obviousness of Inventions*, 50 WM. & MARY L. REV. 989, 1010 (2008) ("Under the time and evidentiary constraints the PTO faces, examiners may have no choice but to accept [applicant] affidavits uncritically. This is unfortunate. Because these affidavits will not be subject to cross-examination or to rebuttal by an expert proffered by an opponent, they will frequently prove to be unreliable evidence, and if they are unrebuttable they will make it fairly easy for applicants to establish nonobviousness.").

[214] Valoir, *supra* note 46 (setting forth the strategy for the same inventor to build a case for unexpected results from a secondary patent). *See generally* Song & Han, *supra* note 101; *see also* Vandana Prajapati & Harish Dureja, *Product lifecycle management in pharmaceuticals*, 12 J. MED. MARKETING 150, 150 (2012) ("Franchise can be sustained if brand equity (and prescriptions) can be transferred to a follow-on or derivative product, even a reformulation or new delivery system. This is generally done through secondary patents or second generation patent."). *See generally* Michael Enzo Furrow, *Pharmaceutical Patent Life-Cycle Management After* KSR v. Teleflex, 63 FOOD & DRUG L.J. 275 (2008) (discussing approaches to overcoming § 103 patentability challenges to pharmaceutical product modification claims).

[215] *Cf.* Amy Motomura, *The Overlooked Significance of Own Prior Art* (on file with author); *see also* Roger Allan Ford, *Patent Invalidity Versus Noninfringement*, 99 CORNELL L. REV. 71, 106-09 (2013) (discussing patentees' informational advantages over defendants with respect to prior art).

[216] 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, at *24-26 (D.N.J. Mar. 29, 2012), *aff'd*, 498 F. App'x 999 (Fed. Cir. 2013) (mem.).

[217] *Id.* at 26-30.

[218] *Id.* at 49.

observed that "the testimony regarding a reduction in sedation when using Seroquel XR is consistent with the results of two trials comparing Seroquel IR and Seroquel XR conducted by AstraZeneca,"[219] which were post-marketing safety-focused trials that the FDA opted to require for this particular pair of drug products pursuant to its so-called "Phase IV" authority to condition approval on such studies when certain pre-requisites are met.[220]

Significantly, the court also credited testimony noting another relative benefit of Seroquel IR, which AstraZeneca established *before* this new form of Seroquel went on the market. This testimony related to the fact that XR can be more rapidly "titrated," or ramped up, to the maximum approved dose than IR.[221] The court explained that, "as compared to Seroquel IR, Seroquel XR shows a significant improvement in the speed with which it can be titrated according to the two drugs' FDA approved labels."[222] Thus, comparative information on titration was developed at the preapproval stage, was reviewed by the FDA, and was placed on the labeling—steps that are in line with this Article's proposal.

All this evidence reasonably bolstered the case for the validity of the Seroquel XR claims, which the court ultimately upheld. The data offered in support of the patent that helped Actavis engineer the switch to Namenda XR presents a different story, which I describe in detail in the next Section. Although the comparative data for Namenda came in during prosecution, not litigation, it is still illustrative of what sorts of evidence might tend to support the case for unexpected results and, therefore, patentability under § 103. More generally, the Namenda XR prosecution history underscores the complex relationship between product-related data and patentability. It shows that the law and institutions involved in determining non-obviousness not only fail to uniformly induce the development of comparative information to establish patentability, but allow for strategies that lead to secondary patents based on questionable "improvement" claims that FDA does not

[219] *Id.* at 50.
[220] 21 C.F.R. § 312.85 (2018) (setting forth the FDA's ability to condition approvals on so-called Phase IV, or post-marketing, studies in certain circumstances); *see also* 21 U.S.C. § 355(o)(3) (2018) (giving the FDA the authority to require post-approval studies when there is evidence of "serious risk"). *But cf.* COMPARATIVE CLINICAL EFFECTIVENESS AND COST-EFFECTIVENESS RESEARCH, *supra* note 60, 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."). *See generally* Charles Steenburg, *The Food and Drug Administration's Use of Postmarketing (Phase IV) Study Requirements: Exception to the Rule?*, 64 FOOD & DRUG L.J. 295 (2006).
[221] *AstraZeneca*, 2012 WL 1065458, at * 50.
[222] *Id.*

see and has not evaluated. The next two sections provide a detailed analysis of that history and, then, a further explication and evaluation of the legal regime that it illustrates.

2. Non-obviousness in the Namenda XR patent prosecution

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. Namenda IR was covered by a patent that Forest had exclusively licensed from a German company called Merz.[223] As noted earlier, this drug was approved for twice-daily administration of 10-mg tablets.[224] One of the primary patents, U.S. Patent No. 5,061,703 ('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"[225] memantine and other, closely related chemical compounds. Although containing method-of-use claims rather than more powerful claims on the chemical entities themselves, the '703 patent made it unscathed through Hatch-Waxman litigation after Forest settled with several generics that challenged its validity.[226] Under the terms of the settlement, the generics were set to enter their market with their versions of memantine as immediate-release tablets in early 2015.[227]

Meanwhile, Forest had filed applications for, and eventually obtained, additional patents related to memantine. These patents cover Namenda XR, which was separately approved by the FDA and which Forest currently markets along with Actavis. Among others, Forest was granted claims that were essentially directed to certain pharmacokinetics—specifically, rates of dissolution and absorption—of memantine in the human body. A representative claim in one of these new patents, U.S. Patent No. 8,039,009 ('009 patent) recites a "method for treating Alzheimer's disease comprising once-daily administration of

[223] *See* New York v. Actavis, PLC, No. 14 Civ. 7473, 2014 WL 7015198, at *10 (S.D.N.Y. Dec. 11, 2014), *aff'd*, 787 F.3d 638 (2d Cir. 2015).
[224] *See supra* notes 128-132 and accompanying text.
[225] *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 compositions of matter, but that does not materially affect the analysis here.
[226] *See, e.g.*, Stipulation and Order, Forest Labs. Inc. v. Lupin Pharm., Inc., 1:08-cv-0021 (D. Del. Sept. 1, 2010), ECF No. 500; Stipulation and Order (D. Del. Sept. 27, 2010), ECF No. 502.
[227] *See* Ben James, LAW360, *Forest, Merz Wrap Up Namenda Patent Litigation* (July 22, 2010), https://www.law360.com/articles/182680/forest-merz-wrap-up-namenda-patent-litigation; *see also* Gregory Dolin, *Do Patent Challenges Reduce Consumer Welfare?*, 83 U. CHI. L. REV. FORUM 256, 267-68 (2017) (discussing such settlements).

a modified release solid oral dosage form" (i.e., a tablet) that included an approximately 28-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 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.[228]

Although it is much more complicated than the quetiapine "gelling agent" claim above, the general 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.[229] 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. As will soon become clear, it is also significant that the claim includes a "once daily administration" limitation.

Not unexpectedly, the closest prior art reference the examiner cited against Forest during prosecution was authored by scientists at Merz, the original assignee of the primary '703 patent—as well as another reference describing "sustained" release formulations of closely related drug compounds.[230] The main reference, Hartmann, was a post-marketing study that described a therapy for Alzheimer's with memantine. In the Hartmann study, "[t]he majority of patients were treated with 20 mg/day memantine, the recommended daily dose," though larger dosages (30 mg and beyond) were used on some patients and apparently safe and well-

[228] U.S. Pat. No. 8,039,009 (filed June 16, 2005), 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*, 716 F. App'x 987 (Fed. Cir. 2017) (nonprecedential). Forest had licensed this second group of patents from another company, Adamas Pharmaceuticals, pursuant to a joint venture agreement.

[229] *See generally* Cramer & Saks, *supra* note 70; Nokhodchi, *supra* note 9.

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

tolerated.[231] Although this aspect of the therapy was not explicitly discussed in the reference, the study's authors had to use multiple doses of 10 mg tablets—because, as in the United States, immediate-release memantine in Germany was approved as a therapy of 10 mg tablets taken twice daily.[232]

Relying on Hartmann in combination with the other reference, the examiner rejected an earlier version of Forest's desired claims covering Namenda XR, which recited "[a] modified release solid oral dosage form for the treatment of Alzheimer's disease comprising about 28 mg of memantine," as obvious after concluding that the publications in totality suggested the "practice of the instantly claimed invention with a reasonable expectation of success."[233] In attempt to overcome the rejection with evidence of unexpected results, the applicant submitted a declaration from a Forest scientist stating that "28 mg memantine modified release was statistically significantly superior to placebo"[234] in treating patients with moderate to severe Alzheimer's, but the examiner maintained the rejection because immediate-release memantine (i.e., Namenda IR) was likewise significantly superior to placebo for this population.[235]

In its next filing, which finally convinced the examiner, the applicant responded with a claim amendment and an argument pointing to a supplemental declaration from the same scientist. The amendment modified the preamble of the claim to "[a] method for treating Alzheimer's disease comprising *once daily administration* of a modified release solid oral dosage form. . . ."[236] The declaration, crucially, "describe[d] that an oral dose of 20 mg memantine as <u>immediate</u> release tablets given *once daily* to Alzheimer's patients was not significantly different from placebo-treated patients"[237]—a result over which a treatment with once-daily 28 mg memantine XR, which *was* better than the placebo according to a prior declaration, was an improvement. The applicant thus urged that the two declarations established that, as

[231] Susanne Hartmann & Hans Jörg Mobius, *Tolerability of memantine in combination with cholinesterase inhibitors in dementia therapy*, 18 INT'L CLIN. PSYCHOPHARMACOLOGY 81, 85 (2003).
[232] *See Clinical Pharmacology and Biopharmaceutics Reviews* at 4, NDA No. 22-525, U.S. FOOD AND DRUG ADMIN., CTR. FOR DRUG EVALUATION AND RES. (Oct. 21, 2009), https://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022525Orig1s000ClinPharmR.pdf
[233] U.S. Pat. App. No. 11/155,330, Non-Final Rejection, at 3 (filed Nov. 1, 2010).
[234] U.S. Pat. App. No. 11/155,330, Response to Office Action, at 7 (filed Dec. 10, 2010).
[235] U.S. Pat. App. No. 11/155,330, Final Rejection (filed Mar. 10, 2011).
[236] U.S. Pat. App. No. 11/155,330, Response to Final Office Action, at 2 (filed Mar. 15, 2011) (emphasis added).
[237] *Id.* (first emphasis added).

amended, "the claimed methods for treating Alzheimer's disease comprising once daily administration of a modified release . . . form comprising about 28 mg of memantine are surprisingly and unexpectedly effective."[238] The examiner then allowed the claims without comment.

It is worth appreciating what got the claims to allowance. The asserted unexpected result was the "improvement" of using a single daily 28-mg extended-release dose over a single daily 20-mg immediate-release dose, a therapy that the FDA has not approved. Indeed, the FDA had approved immediate-release memantine only for a *twice-daily* administration (as two 10 mg tablets).[239] As a matter of establishing relative patient benefit, the correct comparator was of course the actual Namenda IR as approved and prescribed. Indeed, if only one tablet of IR a day were sufficient to treat Alzheimer's, that would mean that patients have been needlessly taking Namenda in two separate 10 mg doses, instead of one 20 mg dose at once.

Nonetheless, this argument, coupled with the aforementioned amendment adding the phrase "once daily administration"—which is what Namenda XR was approved for[240]—sufficed to overcome the rejection. The patent's allowance was followed by a soft switch away from IR, and then a hard switch, during the two years prior to the scheduled generic IR entry in early 2015.[241] The validity of the '009 and related Namenda XR patents has not yet been fully tested in litigation:

[238] *Id.*

[239] *See Approval Package for Application*, NDA No. 21-487, U.S. FOOD AND DRUG ADMIN., CTR. FOR DRUG EVALUATION AND RES. (Oct. 16, 2003), https://www.accessdata.fda.gov/drugsatfda_docs/nda/2003/21-487_Namenda_Approv.pdf.

[240] *See* FDA CTR. FOR DRUG EVALUATION AND RESEARCH, *Clinical Pharmacology and Biopharmaceutics Reviews*, *supra* note 232. The "once daily" limitation does not give generics a meaningful "design-around" opening because they cannot deviate from the dosing approved for the brand under the statutory requirements for ANDA approvals. For example, the generics could not market extended-release memantine accompanied by instructions telling patients to take the two 28-mg tablets every two days, as opposed to a single 28-mg tablet every day. *See* 21 C.F.R. § 314.127(a)(4)(i) (2018).

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

some of the early infringement actions in which they were asserted settled,[242] as has a more recently filed case.[243]

3. Beyond Namenda

Perhaps the most notable upshot of the Namenda XR prosecution is that the examiner's decision to grant the '009 patent to Forest, odd though it may seem from the perspective of a general audience, is not clearly[244] incorrect under substantive patent law. When the publication describing the product, rather than the product itself, is offered as the prior art reference of record, some Federal Circuit authority supports the notion that the formal unexpected results comparison should generally take place between the new product embodying the desired claim and the bare content of the reference.[245] When this is the focus, the difference between real-world utilities of the new and old products, as used for their intended purposes that may be available from sources other than the reference, might not come through.[246]

Indeed, the Namenda XR prosecutor's framing of the unexpected results argument focused on the prior art printed publication, Hartmann, rather than on the prior IR product. Hartmann did not attach any significance to the fact that the treatments it disclosed involved multiple daily administrations, which is a feature of the reference that could perhaps give the prior artisan a reason to believe that a single 20-mg IR

[242] *See, e.g.*, 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* (Sept. 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).

[243] *See, e.g.*, Stipulation to Order of Dismissal Without Prejudice Pursuant to Fed. R. Civ. P. 41(A)(2), Forest Labs., LLC v. Macleods Pharm., Ltd, 1:17-cv-00672-LPS (D. Del. Apr. 3, 2018), ECF No. 38.

[244] "Obviously" might have been a better adverb choice, but was not used above the line for understandable reasons.

[245] *E.g.*, Cadence Pharm. Inc. v. Exela PharmSci Inc., 780 F.3d 1364, 1374-76 (Fed. Cir. 2015) (upholding validity under § 103 based in part on an indirect comparison of results reported in the prior art patent with the testimony regarding results achieved by the subject matter of the patent-in-suit); *see In re* Baxter Travenol Labs., 952 F.2d 388, 391-92 (Fed. Cir. 1991) (concluding that the applicant "has not effectively argued that these particular [desired] claims differ from what is disclosed" in the prior art reference and thus failed to establish unexpected results); *see also* Millennium Pharm., Inc. v. Sandoz, Inc., 862 F.3d 1356, 1368 (Fed. Cir. 2017) ("Unexpected results are shown in comparison to what was known, not what was unknown . . . . [Plaintiff] was not required to create the glycerol ester, when the product has not been created in the prior art.") (citations omitted).

[246] *Cf. In re* Hoch, 428 F.2d 1341, 1343-44 (C.C.P.A. 1970) (focusing on real-world utilities of claimed compounds as compared to those in the prior art).

dose would have treated Alzheimer's just as well. Based on this line of reasoning, the fact that a single 20-mg IR dose does not actually work but a single 20-mg XR does could perhaps be fairly characterized as surprising. Thus, the focus on what is actually disclosed in the particular reference chosen as the closest prior art, as opposed to the underlying product, has the potential to supplant the full picture of clinically relevant data in the unexpected results inquiry.[247]

Perhaps more troubling still, there is also precedent for the notion that scientific validity of the underlying data, whatever specific aspects of the prior art are being compared to the claimed invention, does not really matter in the unexpected results inquiry. In *Janssen Pharmaceuticals v. Watson Laboratories*, the United States District Court for the District of New Jersey noted that "[d]efendants have not persuaded this Court that a patentee faced with a validity challenge must provide evidence of unexpected results that passes muster under undefined high standards of scientific validity" and, further, faulted the defendant for "trying to insert a scientific validity requirement into Federal Circuit law."[248] As to the defendants' argument that "1) the applicant obtained allowance of the [asserted patent] solely on assertions of unexpected results; 2) the applicant relied on [a table containing a flawed cross-study comparison] to persuade the examiner of the unexpected results; and 3) [the table] does not constitute scientifically valid proof of unexpected results,"[249] the trial court responded in part with the following point: "[T]here appears to be hidden in this argument an attempt to shift the burden of proof at this juncture onto Plaintiffs."[250]

The *AstraZeneca* case does provide a counterpoint to these examples. To support non-obviousness of claims covering Seroquel XR, the sponsor provided a credible product-to-product comparison and even

[247] This, to be sure, is a strange result when the prior art reference describes a product that has been approved for use under a particular indication.

[248] Janssen Pharm., Inc., v. Watson Labs., Inc., No. 08-5103 (SRC), 2012 WL 3990221, at *18, 19 (D.N.J. Sept. 11, 2012), *appeal dismissed*, No. 12-1693 (Fed. Cir. Mar. 28, 2013). *But see* Allergan, Inc. v. Teva Pharm. USA, Inc., No. 2:15-cv-1455-WCB, 2017 WL 4803941, at *27-29 (E.D. Tex. Oct. 16, 2017) (adopting a contrary approach); *see also* Duramed Pharm., Inc. v. Watson Labs., Inc., No. 3:08-cv-0116, 2011 WL 2446578, at 6* (D. Nev. June 16, 2011) ("[T]here is insufficient evidence before the court that [the claimed drug] was better than other drugs on the market, including its own product . . . , at preventing breakthrough bleeding. This is evidenced by the fact that the FDA did not allow Duramed to market this proclaimed benefit."), *aff'd*, 438 F. App'x 898 (Fed. Cir. 2011) (mem.).

[249] *Janssen Pharm.*, 2012 WL 3990221, at 20.

[250] *Id.*; *see supra* note 114 (explaining that issued claims must be proved invalid by clear and convincing evidence in district court).

FDA-vetted pre-approval[251] data illustrating an advantage of XR over IR with respect to titration—even though, formally, the closest prior art reference of record was the prior art IR *patent*, not the product.[252] Besides the intuition that it just seems wrong to turn a blind eye to product-to-product comparison evidence, when it is available, to establish unexpected results, there is authority behind a product-focused analysis of unexpected results as well.[253] For example, as the Court of Customs and Patent Appeals explained in *In re Payne*, "[a] prima facie case of obviousness based on structural similarity is rebuttable by proof that the claimed compounds possess unexpectedly advantageous or superior properties. Direct or indirect comparative testing between the claimed compounds and the closest prior art may be necessary."[254] The *Payne* court went on to review the PTO's evaluation of the applicant-submitted data on prior art compounds and those embodying the claims, including a comparative analysis of the compounds' utilities for their intended purpose—"activity against aphid and housefly."[255]

[251] Consistent with general usage in this field, terms "pre-approval" and "premarket" are used interchangeably in this Article. In theory, however, a sponsor could develop data after approval, but before marketing. The goal of this Article's proposal is to have the FDA examine comparative data, so "pre-approval" is the technically correct term.

[252] 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, at *38-44 (D.N.J. Mar. 29, 2012), *aff'd*, 498 F. App'x 999 (Fed. Cir. 2013) (mem.).

[253] *See, e.g.*, *In re* Efthymiopoulos, 839 F.3d 1375, 1378-79 (Fed. Cir. 2016) (focusing on the lack of real-world significance of the proffered unexpected results data in concluding that this evidence should be discounted); Galderma Labs., L.P. v. Tolmar, Inc., 737 F.3d 731, 739 (Fed. Cir. 2013) (focusing on differences in tolerability of claimed and prior art products as marketed); *In re* De Blauwe, 736 F.2d 699, 705 (Fed. Cir. 1984) (requiring experimental data relating to products disclosed by prior art when used for their intended purpose); *cf.* Allergan, Inc. v. Teva Pharm. USA, Inc., No. 2:15-cv-1455-WCB, 2017 WL 4803941, at *28 (E.D. Tex. Oct. 16, 2017) ("[A] clinician might be concerned about bare results, even when they have not been subjected to statistical analysis, and may take action based on those bare results in the absence of the availability of more concrete confirmation that those results are meaningful. But subjective impressions created by bare results are not the appropriate measure by which to compare the efficacy of two different doses of an active ingredient in a testing environment.").

[254] 606 F.2d 303, 315-16 (C.C.P.A. 1979) (citations omitted). The phrase "prima facie" refers here to the structure of the non-obviousness inquiry during patent prosecution. The applicant can rebut the PTO's prima facie showing of "structural obviousness" of the claimed compound with evidence of unexpected results. *See id.* at 314-16.

[255] *Id.* at 316; *cf.* McNeil-PPC, Inc. v. L. Perrigo Co., 337 F.3d 1362, 1370 (Fed. Cir. 2003) ("[T]he [district] court found that the results of clinical studies adduced by McNeil were inconsistent, not shown to be reproducible, and did not include comparative data vis-à-vis placebos or other antidiarrheal/antiflatulent combinations necessary to demonstrate unexpected or synergistic effects."); *In re* Merck & Co., 800 F.2d 1091, 1099 (Fed. Cir. 1986) ("In the absence of evidence to show that the properties of the compounds differed in such an appreciable degree that the difference was really unexpected, we do not think that the Board erred in its determination that appellant's evidence was insufficient to rebut the prima facie case. The fact that amitriptyline and imipramine, respectively, helped some patients and not others does not appear significant.").

Nonetheless, the Namenda prosecution history and the seemingly more permissive[256] line of authority that it reflects makes clear the larger point that patent law does not uniformly provide the incentive to generate comparative data useful to market participants, nor, indeed, do decision-makers consistently base patentability decisions on such data in the context of pharmaceutical product changes. While this sort of information is often considered in patent cases, it does not necessarily have to consist of "real-world" (i.e., product-relevant and clinically relevant) information and the submissions that do come in are analyzed by institutions—the PTO and courts—whose expertise is not focused on clinical trials anyhow. Indeed, the Namenda XR patent prosecution and the *Janssen* case reflect a state of affairs that is arguably worse than the alternative approach under which comparative utility were simply irrelevant for patentability. Instead of adhering to a simple rule that "patented doesn't mean better" and sending a clear "buyer-beware" message that this rule would imply, we allow government imprimatur to be attached to comparative claims of dubious relevance to medical care and sometimes of dubious scientific validity, full stop.[257]

There is a governmental agency, the FDA, that has the expertise to scrutinize comparative data that may have clinical relevance, but under the current legal regime this agency does not generally get to use it unless the sponsor, such as AstraZeneca with its XR/IR titration comparison, decides to go beyond the basic drug approval requirements. While 21 U.S.C. § 372(d), the FDA-PTO cooperation provision discussed in the Introduction,[258] could be a vehicle for getting the FDA involved in looking at comparative results on the patentability side, this solution does not seem altogether satisfying. During prosecution, the data can be of intrinsically limited quality given the early stage of product development during that time,[259] precluding a robust comparative utility analysis even if the FDA were helping the PTO with the examination. During litigation, when more developed data is more likely to be available, § 372(d) does not apply and courts must rely on party experts in evaluating the data in the shadow of the presumption of validity[260]—assuming that applicable precedent even requires that the patentee provide the proper product-to-

[256] Permissive, that is, with respect to the type of comparison the applicant can make to support an argument for non-obviousness.
[257] *See infra* note 315 and accompanying text (discussing unjustified perception of superiority of drugs based on the existence of a patent).
[258] *See supra* notes 80-83 and accompanying text; *see also* Darrow, *supra* note 49, at 401-402. I thank Professor Jonathan Darrow for helpful discussions of this provision.
[259] *See* Eisenberg, *supra* note 50, at 395-96.
[260] *Cf. supra* note 114 and accompanying text (discussing the option to challenge brand patents in the PTAB).

product comparison and, indeed, introduce unexpected results data that has scientific validity.

In spite of the various legal and institutional limitations, the proffered comparative utility information that the PTO and the courts do see can have a critical impact on patentability and, as a result, can in effect enable the sponsor to market the follow-on drug exclusively.[261] This regulatory lacuna is partly responsible for generating perverse incentives for patent-driven product-hopping onto new drug formulations lacking demonstrated clinical differences from the old. Although one possible course correction might be to overhaul substantive patent law and equip the PTO with the tools to induce development of clinical trial data, my sense is that such massive systemic change would be very difficult, if not impossible, to accomplish. Such reform would require effectively remaking the PTO in the FDA's image and, perhaps, a significant course-correction in the doctrine of unexpected results.

In addition, even if logistically possible and potentially beneficial to the patent system as a whole, such reform of patent law and institutions writ large might simply might not be, perhaps somewhat ironically, worth the associated switching costs. This is because the product-hopping problem has largely arisen due to, and reflects, the unique regulatory features of the pharmaceutical industry, which include preapproval, the ANDA pathway, and generic substitution[262]—and so it stands to reason

[261] Interestingly, India appears to have adopted the approach that makes comparative efficacy a requirement of *patentability*, with its courts holding that a modification of a known chemical compound for which an improvement in efficacy is not shown is obvious as a matter of that country's patent law. Novartis AG v. Union of India, AIR 2013 SC, App. No. 2706-2716 of 2013, http://supremecourtofindia.nic.in/outtoday/patent.pdf. *See generally* 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); *see also* Janice M. Mueller, *The Tiger Awakens: The Tumultuous Transformation of India's Patent System and the Rice of Indian Pharmaceutical Innovation*, 68 U. PITT. L. REV. 491, 550-59 (2007). Putting to one side the issue of practical and institutional constraints (e.g., availability of data and the limits of the PTO and courts) that make this approach difficult to execute in practice, I emphasize here that this Article's proposal for comparative analysis at the FDA differs from India's in another crucial respect: it requires a comparison with a product that was actually approved and marketed by the same sponsor, as opposed to a prior art disclosure generally. For critiques of India's approach, see Holman et al., *supra* note 154, at 141; Kevin Tarsa, Novartis AG v. Union of India*: Why the Court's Narrow Interpretation of Enhanced Efficacy Threatens Domestic and Foreign Drug Development*, 39 B.C. INT'L & COMP. L. REV. E. SUPP. 40 (2016).

[262] To be sure, the general problem of patented innovation that may be used to impede competition has been identified in other contexts. *See, e.g.*, Bernard Chao, *Horizontal Innovation and Interface Patents*, 2016 WIS. L. REV. 288 (arguing that anticompetitive product changes accompanied by patenting occur in industries other than pharmaceuticals); Price, *supra* note 43 (more generally exploring the problem of potentially harmful novelty;) *see also* Carlos Acuña-Quiroga, *Predatory Innovation: A Step Beyond? (Understanding Competition in High-technology Markets*, 15 INT'L REV. L. COMPUT. & TECH. 7 (2001). Nonetheless, other industries lack regulatory features such as

to fix it with a regulatory solution that is also pharma-specific.[263] Thus, the approach I adopt in this Article leaves patent law alone, and directly enlists FDA's expertise to undertake a comparative analysis of utility of related drugs independently from the PTO and courts.

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To complete the Namenda story, it should be noted that the sponsor did perform some comparative work, though it was not helpful in differentiating XR and IR. While conducting 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.[264] But that assessment 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.[265]

Thus, at the time of the attempted switch, there was "no study addressing the comparative efficacy of IR and XR,"[266] and specifically "the clinical impact of [XR's distinct] pharmacokinetic properties is not known since it has not been studied in clinical trials."[267] Moreover, a post-marketing study found that 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."[268] This

generic substitution that make the product-hopping problem particularly salient in the pharmaceutical sector, and they also lack the unique market deficiencies discussed in Part III.

[263] *But see* Dan L. Burk & Mark A. Lemley, *Is Patent Law Technology-Specific?*, 17 BERKELEY TECH. L.J. 1155 (2002) (contending that patent law already has industry-specific rules, particularly in areas such as non-obviousness of chemical composition claims).

[264] *See Summary Review* at 3-4, NDA No. 22-525, *Approval Package for Application*, NDA No. 21-487 (June 21, 2010), https://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022525Orig1s000SumR.pdf.

[265] *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. *Medical Review(s)* at 8, 89, NDA No. 22-525, U.S. FOOD AND DRUG ADMIN., CTR. FOR DRUG EVALUATION AND RES. (June 15, 2010), https://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022525Orig1s000MedR.pdf. Certain comparative 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.

[266] *Dosing for Patients Currently Taking Namenda*, NAMENDAXR, http://www.namendaxrhcp.com/patients-currently-taking-namenda.aspx (last visited July 9, 2018).

[267] Deardorff & Grossberg, *supra* note 15, at 3276.

[268] *Id.* at 3267; *see also id.* at 3276. Professors Deardorff and Grossberg also make clear that "[o]ne economic analysis that has not been performed is the comparison of memantine ER and

conclusion calls to mind an observation made by Blue Cross Blue Shield in a comment after a recent public FDA hearing: "There are anecdotal signs that 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."[269] Needless to say, the data presented to the PTO during the prosecution of the Namenda XR patents does not speak to these issues.

In the ideal world, the Namenda strategy would be punished by the market. Although patent law, the primary driver of innovation in this area, does not always pass judgment on the relative quality of inventions, consumers certainly can. Various features of pharmaceutical markets, however, make rational decision-making difficult. Dr. Kessler voiced a concern with this dynamic 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"[270]—that is, brand companies' desire to charge higher drug prices thanks to follow-on patent protection. This is indeed what happened with Namenda XR, as significant numbers of prescribers made the transition away from IR, even before the hard switch, and apparently without evidence that would support this change.[271] The Part that follows describes some of the pathologies that make strategic product hops possible even in soft switch scenarios.

memantine IR in combination with [other drugs] since no studies have been performed comparing the two drugs." *Id.* at 3276.

[269] Comments of Blue Cross Blue Shield Association at 3, *Administering the Hatch-Waxman Amendments: Ensuring a Balance Between Innovation and Access*, *supra* note 80, https://www.regulations.gov/document?D=FDA-2017-N-3615-0087; *see also* Matthew E. Falagas et al., *Compliance with Once-Daily versus Twice or Thrice-Daily Administration of Antibiotic Regimens: A Meta-Analysis of Randomized Controlled Trials*, 10 PLOS ONE e0116207, at 11 (2015) (cautiously concluding that, "considering the limitations surrounding this meta-analysis once-daily antibiotic treatment might be associated with higher compliance than treatment administered multiple times daily in specific populations, for specific sites of infections and specific classes of antibiotics"). A point of note with respect to the Falagas study is that the FDA requires proof of non-inferiority for approval of antibiotics. *See, e.g.*, *Non-Inferiority Clinical Trials to Establish Effectiveness: Guidance for Industry*, *supra* note 61.

[270] Kessler, *supra* note 71, at 437.

[271] *See supra* notes 266-268 and accompanying text.

III. PRODUCT HOPPING AND PHARMACEUTICAL MARKET DEFECTS

Informational inefficiencies in the market for prescription drugs have been well-documented,[272] but are worth recapping here to underscore the need for comparative information in the product switch context and to highlight its potential utility for this relatively well-defined scenario presenting an information gap. The causes of the inefficiencies can be divided roughly into three categories. The first set of limitations has to do with some economic misalignments in this market that can lead to acceptance of more expensive products without a full inquiry into whether there is adequate evidence for the change. The second concerns patent-driven structural limitations, already alluded to earlier in the Article,[273] that limit meaningful competition over follow-on forms of a particular drug. The third relates to cognitive and practical constraints, intensified by vigorous advertising and the credence-good nature of pharmaceuticals, on rational decision-making in this market. These features of the market work together to contribute to the underproduction of socially valuable comparative data and can lead to strategic product hops.[274]

A. Economic Incentives

Analysis of economic limitations relevant to product hopping begins with the insight of "price disconnect."[275] When a physician prescribes a drug, the patient rarely pays the full cost of the drug out of pocket. Instead, a third-party payer, such as the patient's insurer, largely covers the expense in the usual case.[276] The physician, of course, does not pay for the drug either—and, in the absence of a clear signal of the merits or demerits of the new and more expensive version, may in fact be motivated to prescribe it out of the belief that the modification represents the state of the art, providing greater patient benefit and perhaps

[272] *See, e.g.*, Micah L. Berman, *Manipulative Marketing and the First Amendment*, 103 GEO. L.J. 497, 537 (2015); Carrier & Shadowen, *supra* note 7, at 182-89; Darrow, *supra* note 49, at 364-85; *see also* JOHN R. THOMAS, PHARMACEUTICAL PATENT LAW 763 (3d ed. 2015).
[273] *See supra* notes 165-175 and accompanying text.
[274] *Cf.* M. Gregg Bloche, *The Emergent Logic of Health Law*, 82 S. CAL. L. REV. 389, 445 (2009) (arguing that "[r]esearch into the comparative efficacy of tests and treatments is a classic public good"); Kapczynski & Syed, *supra* note 58, at 1952 (explaining why comparative effectiveness research is "highly nonexcludable" and therefore under-incentivized by tools like patents).
[275] Carrier & Shadowen, *supra* note 7, at 168-69; *see also* David H. Kreling, *Market for Pharmaceuticals* 281, 302, *in* PHARMACEUTICAL PUBLIC POLICY, *supra* note 126 ("The demand for pharmaceuticals is not determined by the consumer, but directed by prescribers, and the demand is inelastic with respect to price."); *see also id.* at 299 ("A lack of available comparative value information and a low awareness of drug cost levels by physicians also contribute to reduce the role that price plays in physician prescribing decisions.").
[276] Carrier, *supra* note 26, at 1017-18.

minimizing the risk of a malpractice suit.[277] Thus, because it is often the case that neither doctors nor patients "feel" drug price changes,[278] one court explained in an ongoing antitrust product-hopping case that "the ordinary market forces that would allow consumers to consider price when selecting a product are derailed."[279] Indeed, the widely enacted generic substitution laws reflect the existence of the price disconnect problem even in a context in which the competing suppliers provide products that are basically identical,[280] suggesting that the problem is likely to be greater when drug versions differ. Although proposals to control health care spending from the demand (i.e., patient and prescriber) side have been made[281] and the Affordable Care Act includes provisions that might further this goal,[282] the problem has proven difficult to address as a general matter.

On the payer side, incentives appear to be in place to control costs, but they too can be dampened by informational gaps and other forces. Professor Russell Korobkin explained that "dearth of information makes it extremely difficult for any insurer interested in marketing a policy that covers treatments that satisfy a cost-effectiveness standard to identify ex ante which treatments are, in fact, cost-effective."[283] In addition,

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[277] *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 274, 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."); Korobkin, *supra* note 58, at 541-42 (discussing "defensive medicine"); 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); *cf.* Sheeley v. Memorial Hosp., 710 A.2d 161, 166-67 (R.I. 1998) (holding that the standard of care in medical malpractice cases should be determined by national custom).

[278] *See* Carrier & Shadowen, *supra* note 7, at 169-70, 179-80; Jessie Cheng, Note, *An Antitrust Analysis of Product Hopping in the Pharmaceutical Industry*, 108 COLUM. L. REV. 1471, 1509 (2008); *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* Wendy Netter Epstein, *Nudging Patient Decision Making*, 92 WASH. L. REV. 1255 (2017).

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

[280] Carrier & Shadowen, *supra* note 7, at 204 ("The price disconnect is the economic premise around which all states and the federal government have for the past forty years built a robust generic-substitution regulatory regime.").

[281] *See, e.g.*, David Orentlicher, *Controlling Health Care Spending: More Patient "Skin in the Game?"*, 13 IND. HEALTH L. REV. 348 (2016); *see also* Epstein, *supra* note 278; Rachel E. Sachs, *Delinking Reimbursement*, 102 MINN. L. REV. 2307 (2018).

[282] *See* David Orentlicher, *Cost Containment and the Patient Protection and Affordable Care Act*, 6 FLA. INT'L U. L. REV. 67, 71-76 (2010) (discussing some of these provisions).

[283] Korobkin, *supra* note 58, at 551; *see also* Darrow, *supra* note 49, at 375.

government-based payers are sometimes legally forbidden from refusing to reimburse physician-prescribed treatments,[284] and legal constraints can limit private payers as well.[285] As a result, "health insurers now generally pay for any treatment recommended by a treating physician that offers the potential for any positive clinical benefit unless explicitly excluded from the contractual scope of coverage."[286] Summarizing this state of affairs in health care coverage generally, Professor Wendy Netter Epstein noted that "[u]nnecessary care is consumed because doctors prescribe it, patients consent to it, and payors pay for it."[287]

Insurance companies, to be sure, typically use the services of so-called Pharmacy Benefit Managers (PBMs), which can rely on the threat of exclusion of drugs from formularies—lists of drugs approved for reimbursement—so as to elicit comparative drug data from manufacturers.[288] In addition, PBMs can create formulary "tiers," which are structured so as to pass some of the cost of a more expensive drug option, if selected, onto patients.[289] But PBMs have also been criticized for making deals with manufacturers that had the effect of reducing generic penetration.[290] As Professors Jonathan Darrow and Aaron Kesselheim have noted, the prescription drug market is characterized by "[p]ricing [that] is obscured by a labyrinthine system of rebates, spreads, discounts, coupons, and nontransparent business arrangements,

[284] *See generally* Sachs, *supra* note 281. Notably, however, the state of Massachusetts is considering adopting a "closed formulary" approach to Medicaid reimbursements that would take cost-effectiveness of drugs into account. Nicholas Bagley & Rachel Sachs, *Massachusetts Wants To Drive Down Medicaid Drug Costs: Why Is The Administration So Nervous*, HEALTH AFF. BLOG (Apr. 5, 2018), https://www.healthaffairs.org/do/10.1377/hblog20180404.93363/full; *see also* Rachel Sachs et al., *Value-Based Pricing for Pharmaceuticals in the Trump Administration*, HEALTH AFF. BLOG (Apr. 27, 2017), https://www.healthaffairs.org/do/10.1377/hblog20170427.059813/full.

[285] *See* Korobkin, *supra* note 58, at 547.

[286] *Id.*

[287] Wendy Netter Epstein, *The Health Insurer Nudge*, 91 S. CAL. L. REV. 593, 596 (2018); *see also* Korobkin, *supra* note 58; Saver, *supra* note 277.

[288] Stephen Fink & Mark J. Lewis, *The Myth of "Price Disconnects" in US Pharma Markets*, LAW360 (May 17, 2016), https://www.law360.com/articles/796876/the-myth-of-price-disconnects-in-us-pharma-markets; *see also The AMCP* Format *for Formulary Submissions: Version 4.0*, http://www.amcp.org/FormatV4 (Apr. 2016); *AMCP* Format *Expands Evidence Requirements for U.S. Payers*, ANALYSIS GROUP, http://www.analysisgroup.com/amcp-format-expands-evidence-requirements-us-payers (last visited July 9, 2018).

[289] Fink & Lewis, *supra* note 288.

[290] *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; Michael Hiltzik, *How "price-cutting" middlemen are making crucial drugs vastly more expensive*, L.A. TIMES (June 9, 2017), http://www.latimes.com/business/hiltzik/la-fi-hiltzik-pbm-drugs-20170611-story.html.

particularly between pharmacy benefit managers and manufacturers."[291] As a result, the efforts of PBMs have not consistently contributed to the production of premarket information useful for differentiating between new and old versions of drugs.[292]

Other strategies for creating pressures on drug prices from the demand side include step therapy, which requires that the patient be prescribed the cheaper drug option first and only be allowed to move on to the more expensive one if the former proves ineffective, and prior authorization, which mandates that a physician receive an approval from the payer before prescribing a particular drug.[293] Nonetheless, leaving aside the fact that these measures cannot generally be taken by public payers,[294] it is not clear whether step therapy or prior authorization have contributed extensively to the generation of premarket comparative data that could be helpful in differentiating the benefits of related drug products at the adoption stage,[295] let alone data that has received

[291] Jonathan J. Darrow & Aaron S. Kesselheim, *Promoting Competition to Address Pharmaceutical Prices*, HEALTH AFF. (Mar. 15, 2018), https://www.healthaffairs.org/do/10.1377/hpb20180116.967310/full; *see also* Joseph S. Ross & Aaron S. Kesselheim, *Prescription-Drug Coupons—No Such Thing as a Free Lunch*, 369 NEW ENG. J. MED. 1188 (2013).

[292] *See generally* Corinna Sorenson et al., *Advancing Value Assessment in the United States: A Multistakeholder Perspective*, 20 VALUE IN HEALTH 299, 299, 300 (2017) (noting that, in spite of cost pressures, comparative data on the "net benefits" of various drugs has been difficult to come by); *see also id.* at 305 (explaining that "consideration of observational data in value assessments of asthma therapies could capture the preferences and outcomes of important patient subgroups, such as smokers and patients with serious comorbidities and/or adherence problems, that are not often studied in premarket clinical trials"); *see also* Robin Feldman, *Perverse Incentives: Why Everyone Prefers High Drug Prices—Except for Those Who Pay the Bills*, HARV. J. ON LEGIS. (forthcoming 2019), https://ssrn.com/abstract=3162432 ("[A]lthough we might hope that the insurer would push back on behavior that entrenches higher priced drugs, the incentives that are misaligned and the information that might drive them in that direction is incomplete.").

[293] Fink & Lewis, *supra* note 288; Shepherd, *supra* note 27, at 691.

[294] *See* Sachs, *supra* note 281; *see also* Henry Waxman et al., *Getting to the Root of High Prescription Drug Prices: Drivers and Potential Solutions* at 14-15 (July 2017), available at https://www.ftc.gov/system/files/documents/public_comments/2017/12/00389-142575.pdf (arguing, among other things, for reforms in reimbursement approaches by public payers).

[295] *See* Nikolas H. Goldberg et al., *Availability of comparative efficacy data at the time of drug approval in the United States*, 305 J. AM. MED. ASS'N 1786, 1788-89 (2011) (in a study of newly approved drugs containing new molecular entities, finding that comparative effectiveness information at the time of approval was absent for a significant number of new drug products, and even when present, the information was not always accessible). The authors conclude that "[s]trategies are needed to enhance the accessibility of, and ultimately the use of, this information, particularly in the early marketing experience, when comparative effectiveness data from other sources are scarce or nonexistent." *Id.* at 1789. There is no indication as to whether the situation with respect to comparative data availability is better, or worse, for "hopped" drug products as opposed to new molecular entity products the authors examined. *Cf.* Downing et al., *supra* note 62, at 373-74. The number determined in the Goldberg et al. study, moreover, include new drugs for whose approval the FDA requires an active comparator. Goldberg et al., *supra*, at 1787-88; *see also* Sebastian Schneeweiss et al., *Assessing the Comparative Effectiveness of Newly Marketed Medications: Methodological Challenges and Implications for Drug Development*, 90

meaningful scrutiny.[296] Although these measures have surely aided in the generation of post-approval comparative effectiveness information, which has the advantage of being drawn from actual clinical experiences rather than from clinical trials,[297] the importance of premarket data should not be minimized.[298] Such data can provide concrete evidence for whether a more expensive drug is actually worth switching to, help shape downstream comparative research,[299] and, ultimately, guide the market to rationally accept or reject drug modifications in combination with any available post-marketing data, which may have gaps of its own.[300]

B. Structural Limitations

As discussed in Part II, competition for follow-on innovation between the inventor of the pioneering drug and other firms can often be limited because of broad primary patents, undisclosed know-how, and the

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CLIN. PHARM. & THERAPEUTICS 777, 777 (2011); *infra* note 472 and accompanying text (describing non-inferiority trials required for approval of anti-infectives).

[296] Daniel R. Cahoy, *Medical Product Information Incentives and the Transparency Paradox*, 82 IND. L.J. 623, 635-36 (2007) ("Companies may disclose clinical information directly through a variety of means including: websites, annual reports, or letters to physicians. . . . Of course, the extent to which this may result in the selective disclosure of favorable information is an issue of concern for both the regulatory and financial communities. Further, the results of voluntarily disclosed studies are usually briefly summarized at best and one cannot realistically conduct an independent evaluation of the information.") (citations omitted).

[297] *See* Ryan Abbott & Ian Ayres, *Evidence and Extrapolation: Mechanisms for Regulating off-Label Uses of Drugs and Devices*, 64 DUKE L.J. 377, 396 (2014) (recounting the expansion of post-marketing commitments legally required of pharmaceutical companies). *But cf.* Joshua Cohen et al., *Compared to US Practice, Evidence-Based Reviews in Europe Appear to Lead to Lower Prices for Some Drugs*, 32 HEALTH AFF. 762 (2013) (noting that Europe is ahead of the U.S. in terms of post-marketing comparative drug evidence development); *see also Comparative Effectiveness and Patient-Centered Outcomes Research: Enhancing Uptake and Use by Patients, Clinicians and Payers*, PHRMA FOUND. (Jan. 26-27, 2017), http://www.phrmafoundation.org/wp-content/uploads/2017/01/CER-Conference-Summary.pdf (discussing gaps in comparative drug information).

[298] *See infra* notes 385-397 and accompanying text; *see also* Kazuo Ijima et al., *Time Series Analysis of the Effectiveness and Safety of Capsule Endoscopy between the Premarketing and Postmarketing Settings: A Meta-Analysis*, 11 PLOS ONE e0153662, at 2 (2016) (cataloguing some advantages of post- over pre-marketing comparative studies but ultimately describing them as "complement[ary]").

[299] Alexander & Stafford, *supra* note 58, at 2488; *see also* Schneeweiss et al., *supra* note 295, at 784 ("Although the goal of [comparative effectiveness research]—to understand the relative effectiveness of medical products in routine care—implies evaluation before market entry, parts of the process can be initiated prior to approval."); *cf.* Rebecca S. Eisenberg & W. Nicholson Price, II, *Promoting health care innovation on the demand side*, 4 J. L. & BIOSCI. 3, 18 (2017) (positing why such information is often underproduced).

[300] Although pre-approval data can be of more limited value than the "real-world" data 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. Florence T. Bourgeois et al., *Premarket Safety and Efficacy Studies for ADHD Medications in Children*, 9 PLOS ONE e4102249 (2014); *see also supra* note 60 and accompanying text.

brand's head start advantages.[301] Thus, there may be no one on the supply side to push the brand to build a case driven by premarket data for why patients and prescribers should make the switch to the new version of the drug.[302] Moreover, as a practical matter, robust advocacy for prescribers and patients to stay with (or return to) the original form after the expiration of the primary patent is also infrequently encountered given the previously described generic business model shaped by substitution laws.[303] The brand, therefore, is normally free to promote the modification as vigorously as possible while staying on the legal side of the line without fear of refutation from competitors.[304] While inter-brand competition could potentially serve as a check, evidence developed in many of the antitrust cases involving product-hopping has shown that the original and "hopped" product can be a market unto themselves, without reasonable alternatives for a particular condition offered by drugs with a different active pharmaceutical ingredient.[305]

To further understand the problem, some basic background on drug promotion and advertising is helpful.[306] Like general drug promotion, comparative drug advertising involving printed materials may be subject to the statutory prohibition "of labeling [that] is false and misleading in any particular."[307] An FDA regulation interpreting this and

[301] *See supra* notes 165-175 and accompanying text.
[302] *Cf. supra* notes 173 & 176 and accompanying text (discussing some exceptions).
[303] *See supra* notes 126-127 and accompanying text.
[304] The First Amendment significantly limits the ability of the FDA (or other government agencies) to control such advertising. *See, e.g.*, United States v. Caronia, 403 F.3d 149 (2d Cir. 2012); *see also* Sorrell v. IMS Health Inc., 564 U.S. 552, 557 (2011) ("Speech in aid of pharmaceutical marketing . . . is a form of expression protected by the Free Speech Clause of the First Amendment."); *see also* see Alan Bennett et al., *Back to First Principles: A New Model for the Regulation of Drug Promotion*, 2 J.L. & BIOSCI. 168, 170 (2015); 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). For a discussion of implications of this case law for FDA approval practices, see Patricia J. Zettler, *The Indirect Consequences of Expanded Off-Label Promotion*, 78 OHIO ST. L.J. 1053 (2017). For criticism of this case law and suggestions for reform, see 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); Joshua M. Sharfstein & Alta Charo, *The Promotion of Medical Products in the 21st Century: Off-Label Marketing and First Amendment Concerns*, 314 J. AM. MED. ASS'N 1795, 1796 (2015); *see also* 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.").
[305] New York *ex rel.* Schneiderman v. Actavis PLC, 787 F.3d 638, 658-60 (2d Cir. 2015); *In re* Suboxone (Buprenorphine Hydrochloride and Naloxone) Antitrust Litig., 64 F. Supp. 3d 665 (E.D. Pa. 2014).
[306] *See generally* Alan Lyles, *Pharmaceutical Promotion in the United States* 231, *in* PHARMACEUTICAL PUBLIC POLICY, *supra* note 126.
[307] 21 U.S.C. § 352(a)(1); *see also id.* § 331(a) (defining "[t[he introduction or delivery for introduction into interstate commerce of any food, drug, device, tobacco product, or cosmetic that

related provisions forbids "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."[308] By its terms, however, this regulation does not prohibit non-comparative advertising, or even comparative advertising that does not address safety or efficacy.[309] Thus, Forest's ad campaign touting Namenda XR without directly claiming superiority to IR, conducted through both direct-to-consumer television spots[310] and multi-page spreads in medical trade journals,[311] was lawful. In addition, it was no violation of statute or any FDA regulation for Forest to make statements in press releases like the

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is adulterated or misbranded" as one of the prohibited acts under this section). *See generally* Nathan Cortez, *The Statutory Case Against Off-Label Promotion*, 83 U. CHI. L. REV. ONLINE 124, 126-29 (2017) (surveying the law of misbranding); *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, and thus evidence of "misbranding"). False Claims Act liability is possible in these scenarios as well. *See* 31 U.S.C. § 3729 (2018); *see* Universal Health Servs., Inc. v. United States *ex rel*. Escobar, 136 S. Ct. 1989 (2016).

[308] 21 C.F.R. § 202.1(e)(6)(ii) (2018); *see also id.* § 201.57(c)(2)(iii) ("Any statements [on product labeling] comparing the safety or effectiveness of the drug with other agents for the same indication must, except for biological products, be supported by substantial evidence derived from adequate and well-controlled studies as defined in § 314.126(b) of this chapter unless this requirement is waived under § 201.58 or § 314.126(c) of this chapter.").

[309] *See generally* David A. Kessler et al., *Therapeutic Class Wars: Drug Promotion in a Competitive Marketplace*, 331 NEW ENGLAND J. MED. 135 (1994); *see also* Darrow, *supra* note 49, at 368-69 ("[T]he void of non-biased information is often filled by drug company 'detailers,' who personally visit physicians for the primary purpose of influencing prescribing decisions.") (citation omitted); *id.* at 369 (explaining that "[m]any people (*including [many] physicians*) think that newer drugs are better. While that's a natural assumption to make, it's not true. Studies consistently find that many older medicines are as good as—and in some cases better than—newer medicines." (quoting *Evaluating Statin Drugs to Treat: High Cholesterol and Heart Disease*, CONSUMER REPS. HEALTH BEST BUY DRUGS 1, 21 (2012), http://www.consumerreports.org/health/resources/pdf/best-buy-drugs/StatinsUpdate-FINAL.pdf)) (emphasis in original); *cf.* James J. Dettore et al., *Branding lessons from consumer marketing*, PHARM. EXECUTIVE (May 2001) (discussing the important role of direct-to-consumer marketing and branding in the pharmaceutical industry).

[310] 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); Steenburg, *supra* note 220, at 299 ("[D]irect-to-consumer . . . advertising and other increasingly sophisticated marketing strategies often result in swift transitions from small, controlled trials to widespread use.") (citation omitted); *see also* Dettore et al., *supra* note 309.

[311] *See* DRUG TOPICS 2-4 (Aug. 2013), http://images2.advanstar.com/pixelmags/drug-topics/pdf/2013-08.pdf. The ad does include a disclaimer, in relatively small print, indicating that no comparative study was performed between IR and XR. *Id.* at 2; *see also* Shepherd, *supra* note 27, at 697 & n.222.

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."[312] Although these ads and statements do not mention any evidence, such claims can create something of a snowball effect of apparently unjustified switches.[313]

While advertising can in theory be scrutinized from the demand side, a point that I will address further in the next Section, competition on the supply side can be crucial for helping highlight comparative advantages and disadvantages of related drug products for prescribers and patients. Similarly, pressures from competitors can serve as a third-party check on communications between manufacturers and payers, whose permissible scope has recently been expanded under the 21st Century Cures Act.[314] But because such competition is rare, market participants may be impeded in their ability to identify what may be a largely strategic product hop. Worse yet, the very existence of the patent on the new form of the drug can create an unjustified perception that it is better, in spite of the lack of evidence.[315] These dynamics can contribute to the

[312] 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.

[313] Indeed, even the soft switch was estimated to lead to a transition of a significant number of prescribers and patients to XR. *See* New York *ex rel.* Schneiderman v. Actavis PLC, 787 F.3d 638, 648 (2d Cir. 2015). Partly for the reason that such ads induce unjustified switches to more costly drugs, the American Medical Association called for a ban of direct-to-consumer drug ads. *See AMA Calls for Ban on DTC Ads of Prescription Drugs and Medical Devices*, AM. MED. ASS'N, https://www.ama-assn.org/content/ama-calls-ban-direct-consumer-advertising-prescription-drugs-and-medical-devices (Nov. 17, 2015); *see also supra* note 277 (explaining how physician risk-averseness, particularly in the face of potential malpractice suits, can drive prescribing decisions).

[314] *See* 21 U.S.C. § 352(a); *see also id.* 352(a)(2)(A) ("[T]he term 'health care economic information' means any analysis (including the clinical data, inputs, clinical or other assumptions, methods, results, and other components underlying or comprising the analysis) that identifies, measures, or describes the economic consequences, which may be based on the separate or aggregated clinical consequences of the represented health outcomes, of the use of a drug. Such analysis may be comparative to the use of another drug, to another health care intervention, or to no intervention."). *See generally* Peter J. Neumann, *The FDA's Regulation of Health Economic Information*, 19 HEALTH AFF. 129 (2000) (discussing the statutory regime relating to communication of health care economic information prior to the 21st Century Cures Act, which amended the FDCA); *see also* Sam F. Halabi, *Off-Label Marketing's Audiences: The 21st Century Cures Act and the Relaxation of Standards for Evidence-Based Therapeutic and Cost-Comparative Claims*, 44 AM. J. L. & MED. 181 (2018) (discussing an expansion in the scope of permissible manufacturer-payer communications allowed by 21st Century Cures Act).

[315] *See also* Darrow, *supra* note 49, at 385-87 (describing the "patent halo"); Mansfield, *supra* note 14 (discussing unjustified perceptions of superiority of certain types of new drug versions); *cf.* Evans, *supra* note 60, at 491 ("Today's drug labeling tells only what is known about a drug's risks and benefits but does not give a sense of all that is still unknown. This has contributed to a

underproduction of valuable comparative information, lead to unnecessary and costly switches, and ultimately diminished incentives to make improved products.

C. Cognitive Constraints

Well-documented cognitive constraints, combined with various pressures on prescribers, can reinforce these effects. Returning to the advertising example, it may well be accurate that some caregivers like Namenda XR over IR even though evidence does not support the switch,[316] but busy physicians[317] might not closely scrutinize the claim and erroneously come to believe that XR has replaced IR as the standard of care.[318] The print ad did state in relatively small font that "[t]here is no study addressing the comparative efficacy" of Namenda XR and IR, but medical care providers do not always notice such disclaimers.[319]

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"[320] declaring that "[t]he products in this comparison may or may not be equally effective or safe,"[321] 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."[322] Indeed, "a realistic context statement to a physician-targeted prescription drug ad did not generate sufficient

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culture of mass drug marketing and consumption in which people are eager to get the latest drug, often believing that it must be better and safer than older drugs when in fact, such comparative data rarely exist.") (citing CONG. BUDGET OFF., RESEARCH ON THE COMPARATIVE EFFECTIVENESS OF MEDICAL TREATMENTS 4 (2007), available at http://www.cbo.gov/ftpdocs/88xx/doc8891/12-18-ComparativeEffectiveness.pdf).

[316] *See* Deardorff & Grossberg, *supra* note 15.

[317] *See, e.g.*, Cynthia M. Ho, *First Amendment Overprotection of "Alternative Facts": Cognitive The Case of Cognitive Biases with Pharmaceutical Marketing*, 94 IND. L.J. (forthcoming 2019), https://ssrn.com/abstract=3152645.

[318] *See supra* note 277 and accompanying text (explaining that, based on malpractice concerns and other factors, the real or perceived customary approach for treating certain conditions can drive prescribing decisions). *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 557 (I. Glenn Cohen, Allison Hoffman & William Sage, eds., 2016) (discussing the influence of malpractice law on medical care and the challenge of reform).

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

[320] *Id.* at 195.

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

[322] *Id.* at 195.

awareness of claim caveats to differentiate price-comparison response of those exposed to the context statement from those who were not."[323] Another study showed that journal advertisements and other forms of marketing have a greater effect on physician prescribing decisions than evidence in scientific articles.[324] These findings are consistent with broader claims that so-called "schemas," or biases, and other cognitive limitations—in addition to time constraints—can interfere with sound medical decision-making in the face of drug advertising.[325]

Although examples of limitations on human ability to scrutinize advertising messages can certainly be found outside the prescription drug context, pharmaceutical markets can make for a particularly challenging environment in which to make rational decisions. Drugs are a paradigmatic example of so-called "credence goods," or products whose utility and quality consumers can have difficulty assessing, even after consumption.[326] By their nature, credence goods present the possibility of significant information asymmetries between manufacturers and even sophisticated medical professionals—let alone patients.[327] The information gap, after all, is one of the reasons for the existence of the FDA and the pre-marketing approval process.[328] Thus, when the other defects in this market are combined with powerful advertising and acknowledged cognitive constraints, the lack of transparency with respect to marginal benefits of the new drug version relative to the one that is

[323] *Id.*

[324] 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.").

[325] *See* Ho, *supra* note 317; *see also* Cynthia M. Ho, *Drugged Out: How Cognitive Bias Hurts Drug Innovation*, 51 SAN DIEGO L. REV. 419 (2014) (discussing schemas in another context in the pharmaceutical arena).

[326] Daniel Carpenter, *Confidence Games: How Does Regulation Constitute Markets*, *in* GOVERNMENT AND MARKETS: TOWARDS A NEW THEORY OF REGULATION 164, 173-181 (Edward J. Balleisen & David A. Moss eds. 2009); *see also id.* at 165 ("Evidence from the most rigorous and historically contextual studies suggests that institutions of entry and approval regulation have arisen in markets characterized by learning constraints, including credence good markets and markets with appreciable information asymmetries. In the absence of regulation, as well as in the presence of weak regulation, these markets are characterized by equilibrium fraud and "lemons problems" . . .") (citing George A. Akerlof, *The Market for "Lemons": Quality Uncertainty and the Market Mechanism*, 84 Q.J. ECON. 488 (1970)); Ariel Katz, *Pharmaceutical Lemons: Innovation and Regulation in the Drug Industry*, 14 MICH. TELECOMM. & TECH. L. REV. 1, 11-13 (2007).

[327] Katz, *supra* note 326, at 27-28.

[328] *See generally* CARPENTER, *supra* note 99. Indeed, addressing this market failure in information production is a standard economic justification for FDA regulation. *See, e.g.*, Kapczynski & Syed, *supra* note 58, at 1956-57; *see also* Cahoy, *supra* note 296, at 627 ("An individual's decision regarding the safety profile of a particular product can be manipulated, though, by controlling the information the individual receives."). *See generally* Eisenberg, *supra* note 105.

already being used can cause considerable difficulties for the participants in this market.

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The market, to be clear, has not collapsed. The Seroquel example illustrates that, in spite of these defects, drug modifications can lead to real improvements in patient care.[329] Moreover, in switching from IR to XR, AstraZeneca generated some premarket comparative data on titration—and was apparently also required to conduct post-approval comparative safety trials in this particular case.[330] Other examples when a drug change offered an improvement in the overall quality of care, an advantage for a particular patient subpopulation, or at least a demonstrably different therapeutic profile backed up by data developed pre-approval can be readily found.[331] Nonetheless, antitrust litigation reveals that strategic switches also happen with some frequency. The fact, for example, that Actavis lost in the Second Circuit tells the story: comparative evidence establishing some difference or advantage, if it existed, would have defeated a monopolization claim by supplying a non-pretextual "procompetitive justification" for the change.[332]

To reduce the incidence of such cases, an information-forcing mechanism is needed. I describe a proposal for implementing it, relying on the FDA as an information intermediary,[333] in the Part that follows. Firms that already undertake changes to newly patented products that are actually supported by premarket comparative data is unlikely to be negatively affected by the proposal and, as I explain in Part V, will

[329] *See supra* notes 216-222 and accompanying text.

[330] *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, at *55 (D.N.J. Mar. 29, 2012), *aff'd*, 498 F. App'x 999 (Fed. Cir. 2013) (mem.).

[331] *See, e.g.*, Bourgeois et al., *supra* note 300; Johan C.F. Van Lujin et al., *Superior efficacy of new medicines?*, 66 EUR. J. CLIN. PHARMACOLOGY 445 (2010).

[332] New York *ex rel.* Schneiderman v. Actavis PLC, 787 F.3d 638, 658-60 (2d Cir. 2015).

[333] *See* Rebecca S. Eisenberg, *Patents, Product Exclusivity, and Information Dissemination: How Law Directs Biopharmaceutical Research and Development*, 72 FORDHAM L. REV. 477 (2003); Amy Kapczynski, *Dangerous Times: The FDA's Role in Information Production, Past, and* Future, 102 MINN. L. REV. 2357 (2018); *see also* Laakmann, *supra* note 105, at 147-48, 158-62 (discussing the institutional role of the FDA as an information intermediary); Anna B. Laakmann, *The New Genomic Semicommons*, 5 U.C. IRVINE L. REV. 1001, 1038 (2015) ("The FDA further acts as an information intermediary by using its labeling authority to certify the credibility of drug and device manufacturers' marketing claims. In addition to specifying the type and amount of data that manufacturers must generate before they can communicate with patients and physicians about intended uses of their products, the FDA filters how interpretations of that data are conveyed in product labels.") (citing Eisenberg, *supra* note 105, at 370-72). *But see* Richard A. Epstein, *Against Permititis: Why Voluntary Organizations Should Regulate the Use of Cancer Drugs*, 94 MINN. L. REV. 1, 31-33 (2009) (questioning the FDA's information-forcing role and suggesting reliance on private institutions to generate health care information).

probably be helped by it in some ways.[334] The challenge, of course, is to the firms that do not. While such firms could still sell the modified version—the idea is not to withhold approval for lack of such data[335]—they would be subjected to certain disadvantages. The proposal, then, may end up disincentivizing the development and marketing of drug modifications that,[336] despite the lack of supporting comparative evidence at the time of approval, might have advantageous properties, in general or for some group of patients, that come to light only after some period of use. More globally, the proposal might drive down the amount of research devoted to cumulative innovation in the pharmaceutical space, and thereby reduce the number of drug options available on the market.[337]

While I address the question of potential effects on cumulative innovation in Part V, I emphasize here that firms that decide to forgo the costs of developing comparative data could still market the modified product and potentially achieve some degree of success. Thus, doctors could legally prescribe the new versions[338] and substantiate insurance coverage in various ways: Perhaps, the other options have failed and this is the alternative that remains, or there is particularized evidence that the follow-on version would work better for a specific patient—for example, an extremely forgetful individual for whom a lower pill burden would be critical no matter what the countervailing considerations might be.[339] The goal is only to make clear to the market that, pre-approval, the sponsor developed no comparative data relevant to prescribing decisions so that physicians, patients, and payers can make decisions with this information

[334] *See infra* notes 487-490 and accompanying text.

[335] *See* John Vernon et al., *Fewer Drugs, Shorter Lives, Less Prosperity: The Impact of Comparative Effectiveness Research on Health and Wealth*, 45 DRUG INFO. J. 699, 701 (2011); *see also* 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). *But cf. supra* note 58 and accompanying text (exploring the possibility of using comparative effectiveness as a condition of drug approval).

[336] This point assumes that a patent on the modification can still be obtained, but the stick proposed in Part IV would serve as enough of a counter-incentive to discourage investment into the modification. *Cf.* Shepherd, *supra* note 27, at 702-06 (discussing potentially negative effects on innovation of the antitrust product-hopping case law).

[337] *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); Ross D. Petty, *Limiting Product Choice: Innovation, Market Evolution, and Antitrust*, 21 J. PUB. POL'Y MKTG. 269 (2002).

[338] *See infra* notes 304-313 and accompanying text (describing allowable forms of drug advertising).

[339] Korobkin, *supra* note 58, at 570 (discussing "[t]he problem of individual variation").

in hand.[340] The approach will not fix all the defects in this market, but the knowledge that the new version might not be a demonstrated "state of the art" product after all may sometimes ameliorate some of their consequences,[341] such as unnecessary switches and unjustified spending on higher-priced drugs.[342]

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

As sketched out in the Introduction, the central feature of this Article's proposal is an information-forcing mechanism through a drug's labeling, and particularly via the printed material that comes with the drug as the package insert.[343] The insert provides a centralized repository of information that officials at the FDA's Center for Drug Evaluation and Research have vetted and required the sponsor to include with the drug as marketed for the benefit of prescribers, users, and payers.[344]

Currently, material on the insert includes information such as the drug's approved indication, dosing, side effects, contraindications, patient counseling information, summaries of the clinical studies conducted during the approval process, and so on.[345] The labeling is not always read as carefully as one might hope, but the FDA has taken measures—such as adopting the so-called "Physician Labeling Rule"[346]—in pursuit of an effort to make those inserts somewhat more user-friendly. Moreover, if the labeling is to include new kinds of information such as comparative data, prescribers can be alerted about it through physician education campaigns. The FDA has conducted such campaigns in the past in other contexts, including as part of an effort to

[340] Or, if the sponsor did develop such data, these market participants would proceed knowing what the data shows.

[341] One specific mechanism by which market defects could be ameliorated would be for payers to install the cheaper version as the default. *See* Scott D. Halpern et al., *Harnessing the Power of Default Options to Improve Health Care*, 357 N. ENGL. J. MED. 1340 (2007).

[342] And, further downstream, these dynamics could lead to evidence-driven medical innovation. *See infra* notes 355-360 & 398-410 and accompanying text.

[343] *See* 21 C.F.R. § 201.57 (2018) (describing the content of the labeling that must accompany prescription drug products).

[344] *See* 21 U.S.C. § 352(f) (2018); *Labeling Development Team*, U.S. FOOD AND DRUG ADMIN., https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm443026.htm.

[345] *See* 21 C.F.R. § 201.57 (2018).

[346] *Labeling for Human Prescription Drugs and Biological Products—Implementing the PLR Content and Format Requirements*, U.S. FOOD AND DRUG ADMIN. (Feb. 2013), https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075082.pdf.

inform physicians about cost-saving prescribing options.[347] Finally, even if clinicians fail to examine the information on the inserts,[348] payers can point to it in making coverage decisions. The sections that follow explain precisely what types of data the FDA would seek under this Article's proposal, propose the sticks the agency could rely on to elicit it from sponsors, and note which kinds of drug modifications would fall under the proposed regime, providing implementation details as needed. These Sections also explicate the benefits of the proposal.

A. The Threshold Standard and the FDA's Task

1. Theorizing drug comparisons

Before describing the sticks the FDA could use to nudge companies into the development of comparative data, it is essential to define the nature of the data that the agency should be seeking and the sorts of information that would go on the insert. At the outset, it bears emphasizing that the concepts of drug safety and effectiveness cannot be pinned down with precision in an absolute sense. Although FDA approval of a drug requires "substantial evidence" of safety and effectiveness,[349] the decision whether a product should be allowed on the market given its benefits and risks is ultimately a judgment call that the FDA must make based on this evidence.[350]

Comparative drug benefits are even more difficult to assess because the comparisons can take place across a number of parameters.[351] Between two or more drugs used to treat the same condition, relative

[347] Scott Gottlieb, M.D. & Leah Christl, Ph.D., *FDA Taking New Steps to Better Inform Physicians about Biosimilars Through Education about these Potentially Cost-Saving Options*, U.S. FOOD AND DRUG ADMIN.: FDA VOICE BLOG (Oct. 23, 2017), https://blogs.fda.gov/fdavoice/index.php/2017/10/fda-taking-new-steps-to-better-inform-physicians-about-biosimilars-through-education-about-these-potentially-cost-saving-options.

[348] *See* Evans, *supra* note 60, at 508 ("Communicating risk-benefit information will not improve public health, unless the information actually is applied at the point when physicians prescribe drugs. Labeling changes repeatedly have been shown, in empirical studies, to have little impact on physicians' prescribing behavior.") (first citing Walter Smalley et al., *Contraindicated Use of Cisapride: Impact of Food and Drug Administration Regulatory Action*, 284 J. AM. MED. ASS'N 3036, 3038 (2000); then citing Raymond L. Woosley & Glenn Rice, *A New System for Moving Drugs to the Market*, ISSUES SCI. & TECH. ONLINE, Winter 2005, http://www.issues.org/21.2/woosley.html). Nonetheless, the cited studies precede the introduction of the Physician Labeling Rule. *See* Karen B. Feibus, MD, *FDA's Proposed Rule for Pregnancy and Lactation Labeling: Improving Maternal Child Health Through Well-informed Medicine Use*, 4 J. MED. TOXICOLOGY 284, 284 (2008) ("With development and implementation of the Physician Labeling Rule (PLR), FDA transformed the prescription drug label into a better communication tool in which information is better organized, clearly presented, and more easily located.").

[349] 21 U.S.C. § 355(d).

[350] *See, e.g.*, Cahoy, *supra* note 296, at 627-28.

[351] Bloche, *supra* note 274, at 446 ("Selection of outcome measures for such [comparative] studies is fraught with normative questions that lack agreed-on answers.").

safety or efficacy can vary depending on, for example, the sub-population of the patients under treatment.[352] Two drugs that have different side effects are not readily comparable because such things can be basically incommensurable, and, even in theory, it may be difficult to make an absolute judgment as to which is "better" between two drugs, one of which is the safer and the other, more effective.[353] 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 in making a decision between two drug options make conclusive comparisons between two different drug products difficult.[354] Nonetheless, although data that can enable definitive comparative judgments even between closely related drug products can be difficult to generate, 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 evidence shows some potential for health outcome improvements, but only for particular populations or in certain treatment settings. In particular, when one deals with closely related drug products, the number of potential axes of difference should be reduced, making a comparison more manageable than between drugs with different active pharmaceutical ingredients.

Indeed, 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 form to choose in a particular scenario can still be developed.[355] Consider again the example of Seroquel and the premarket evidence of more rapid titration made possible with XR as opposed to IR: if a patient comes in with an acute episode of bipolar depression, getting to the maximum approved dose as soon as possible may be a critical priority, justifying the use of XR instead of IR.[356] Perhaps because of similar dynamics with other drugs, Dr. Kessler explained the value of examining the correlation between "blood levels of drug over time with the clinical outcomes"[357] when a drug is converted from IR to XR, and

[352] *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).
[353] *See supra* note 60 and accompanying text (discussing terminological differences between "efficacy" and "effectiveness").
[354] *See generally* Saver, *supra* note 277.
[355] *See* Cramer & Saks, *supra* note 70 (discussing potential axes of improvement for extended-release versus immediate-release products).
[356] *See supra* notes 221-222 and accompanying text.
[357] Kessler, *supra* note 71, at 440.

highlighted the need for "clinical results in a variety of populations" taking XR products.[358] Facilitation of tailored treatment decisions is a significant benefit even in cases where the data does not demonstrate that the new product is, to give an example of a standard that the FDA actually uses in another context, "clinically superior"—however this latter standard is to be operationalized.[359] Finally, because drugs are generally modified with particular purposes in mind, and a particular modification type (e.g., switch to an extended-release form) should normally lead to a limited number of expected, specific effects in the functioning of the active pharmaceutical ingredient, researchers could readily form hypotheses based on which differences between the versions would be framed, tested and evaluated.[360]

2. The proposed standard and how to meet it

Since the concept of comparative efficacy is quite indeterminate—perhaps the better term is "clinical distinctiveness" given the challenge of the absolute comparisons—the standard is best left open-ended. Thus, I frame the proposed standard as "data relevant to relative performance of new product versions."[361] Although a permissive-seeming standard, it is still a significant shift from what is currently done. Given the present default of proof of safety and effectiveness over a placebo,[362] the paradigm of using the previous drug as a so-called "active comparator" when a modification takes place might help get firms to think in terms of documented differences in clinical value, rather than only in terms of what can be patented.[363] This standard would also untie

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[358] *Id.*

[359] *See* FDA Reauthorization Act of 2017, Pub. L. No. 115-52, sec. 607(a), § 527(c),(e), 131 Stat. 1005, 1049-50, *codified at* 21 U.S.C. § 360cc(c),(e) (requiring a showing of clinical superiority at the approval stage before recognizing regulatory exclusivity for a so-called orphan drug); *see also id.* § 360cc(c)(2) (defining a "clinically superior" drug as one that "provides a significant therapeutic advantage over and above an already approved or licensed drug in terms of greater efficacy, greater safety, or by providing a major contribution to patient care").

[360] *See, e.g.*, *In re* Kao, 639 F.3d 1057, 1062, 1068-69 (Fed. Cir. 2011) (describing the unexpected result of multiple peaks of blood concentration of the active pharmaceutical ingredient, which prevents patients from building tolerance to the drug); *see also supra* notes 203-214 and accompanying text.

[361] More rigorous standards are possible. *See, e.g.*, *supra* note 359 & *infra* notes 473-474 and accompanying text (discussing a setting in which the FDA must use the "clinically superior" standard). Nonetheless, given the already significant shift toward comparative analysis proposed here and the difficulty of establishing superiority, a more permissive standard is appropriate. In Part V, I discuss the objection that the standard could be readily gamed by sponsors.

[362] *See* 21 C.F.R. § 314.126(b) (2018). Sometimes, to be sure, availability of a new and clearly better drug could render the risk-benefit profile of an already-approved drug no longer acceptable, causing its withdrawal. *See, e.g.*, *infra* notes 453-454 and accompanying text.

[363] *Cf.* 21 C.F.R. § 314.126(b)(iv) (2018) (describing the option of "[a]ctive treatment concurrent control" for approval).

the hands of the FDA, whose officials have shown an interest in performing such inquiries.[364]

A significant number of companies already develop comparative data voluntarily[365] or are required to do so by the FDA in certain special circumstances.[366] A general authority for the FDA to request and analyze comparative drug information, however, could further curb strategic behavior and channel firms toward evidence-based drug modifications. In addition, it is important to grant the FDA the power to evaluate comparative data before marketing because, after approval, the agency loses a measure of control over both the sponsor and the product after marketing.[367]

The FDA's task would be to determine whether the information that the sponsor submitted meets the proposed standard and work with the firm to draft conclusions that it supports under the traditional "substantial evidence" standard.[368] While the entirety of the raw data would not be revealed to the public, the summary of the data and the corresponding conclusions would become part of the product's labeling. If doubts with respect to the information's relevancy remain, FDA officials could request that the sponsor submit a clarifying explanation or, perhaps, further information before settling on the labeling—just as the FDA does during the regular approval process.[369] As with other FDA decisions, third parties could weigh in by filing so-called citizen petitions aiming to persuade the agency that the labeling statements are not fully supported.[370] And if the FDA concludes that the sponsor submitted no relevant information, the agency would then mandate that the sponsor indicate this fact on the labeling in a prominent way.

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[364] *See supra* notes 79-80 and accompanying text.
[365] *See supra* note 295 and accompanying text.
[366] *See, e.g.*, *Non-Inferiority Clinical Trials to Establish Effectiveness: Guidance for Industry*, *supra* note 61.
[367] *See generally* Steenburg, *supra* note 220; *see also* Cahoy, *supra* note 296, at 632-34, 667-70; Kevin Fain et al., *The Food and Drug Administration Amendments Act and Postmarketing Commitments*, 310 J. AM. MED. ASS'N 202 (2013); Kapczynski, *supra* note 333, at 2369-74 (discussing the problem of "incomplete data" that thwarts accurate post-marketing drug comparisons).
[368] *See* 21 U.S.C. § 355(d) (2018); *see also* 21 C.F.R. § 201.57 (2018) (reiterating the statutory standard of "adequate and well-controlled studies" for providing the basis for information on the labeling).
[369] *See generally* Richard A. Merrill, *Regulation of Drugs and Devices: An Evolution*, 13 HEALTH AFF. 48 (1994); *see also* Grabowski & Vernon, *supra* note 100.
[370] *See* 21 C.F.R. § 10.30 (2017). Confidentiality of sponsor data, however, could be a barrier here as in challenges to other FDA decisions. *See, e.g.*, Lisa Heinzerling, *The FDA's Plan B Fiasco: Lessons for Administrative Law*, 102 GEO. L.J. 927, 972 (2014).

If, for its part, the sponsor is dissatisfied with the FDA's decision on the content of the labeling, it could challenge the agency's decision in court under the Administrative Procedure Act[371]—though, to be sure, the courts tend to defer greatly to the FDA on such matters, and these challenges rarely succeed.[372] Of course, the sponsor could also opt out of the system altogether and agree to the "no relevant comparative data was provided" notation at the outset. To reiterate, though, even if the firm chooses not to participate in the data-submission regime or is dissatisfied with the content of the FDA-approved labeling, it is still free to market the product and to convince prescribers to utilize it in spite of the lack of comparative information. Just as it paves the way for advertising of off-label uses generally (as long as truthful and non-misleading),[373] the First Amendment would prohibit sanctions against some types of comparative claims that find support outside the labeling proposed here.[374] Still, as I explain further in the next Section, the required labeling could temper the effects of such advertising.

Significantly, the proposal does not task the FDA with engaging in cost-effectiveness analysis, which would push beyond the agency's core competency of analyzing scientific data and into territory which it has historically been reluctant to enter.[375] Instead, the standard requires only that the agency process and evaluate the submitted data in its role as an information intermediary, and leaves the corresponding financial judgement calls to payers and others. As further discussed in the Section that follows, though, information on comparative clinical effectiveness

[371] 5 U.S.C. § 706(2)(A) (2018).

[372] *See* Steenburg, *supra* note 220, at 334 ("Recognizing their own limitations, courts are unwilling to question the agency's judgment as to the necessary standards for assessing safety and efficacy."); *see also, e.g.*, Cytori Therapeutics, Inc. v. Food & Drug Admin., 715 F.3d 922, 927 (D.C. Cir. 2013) ("[A] court is ill-equipped to second guess this kind of agency scientific judgment under the guise of the [Administrative Procedure Act's] arbitrary and capricious standard.").

[373] Indeed, in a manner analogous to the advertising of "off-label" uses, which is protected by the First Amendment, *see supra* note 304 and accompanying text; *see also* Cortez, *supra* note 307, the sponsor could legally make comparative claims supported by truthful and non-misleading information not vetted by the FDA. Interestingly, though, sponsors currently wishing to make comparative claims often have difficulty meeting the "substantial evidence or substantial clinical experience" standard mandated by 21 C.F.R. § 202.1(e)(6)(ii). *See* Coleen Klasmeier, *Congress Should Clarify the Circumstances Under Which Drug Makers Can Communicate Results on Comparative Effectiveness*, 31 HEALTH AFF. 2220 (2012). The proposed approach clears up this gray area because the FDA will have already weighed in on whether comparative claims are supported by substantial evidence. *See supra* note 368 and accompanying text.

[374] *See, e.g.*, Va. St. Bd. of Pharmacy v. Va. Citizens Consumer Council, Inc., 425 U.S. 748, 770 (1976). For example, even if the insert states that no relevant comparative data was provided to the FDA, sponsors could legally share scientific articles describing studies comparing the drug forms with physicians. *See* Klasmeier & Redish, *supra* note 304.

[375] *But see* David A. Hyman & William C. Kovacic, *Risky Business: Should the FDA Pay Attention to Pharmaceutical Prices?*, 11 N.Y.U. J. L. & LIBERTY 754 (2017) (making the case that the FDA should engage in economic cost-benefit analysis in some circumstances).

can help health care providers and patients make informed decisions with respect to whether a particular treatment is worth the cost—specifically, whether the evidence suggests that the more expensive, on-patent version of the drug may be worth switching to.

Consistent with the open-ended standard proposed here, information acceptable for meeting the proposed standard could come from a variety of study types. Data can of course be very costly to generate, with the randomized head-to-head general safety and efficacy clinical trial being the expensive gold standard for comparisons.[376] Nonetheless, the proposal allows for some relatively inexpensive ways by which firms can surpass the "relevant to relative performance" hurdle. Although the FDA would apply the standard on a case-by-case basis, studies that could qualify under the proposed standard could be satisfied by at least the following types of submissions: (1) for extended-release products and new dosage forms in particular, studies examining and documenting improvements in patient compliance, reduction in the prevalence a signature side effect associated with the original drug, the difference in the impact of food consumption from that on the prior version,[377] titration rates,[378] and so on; (2) for certain products that embody "purer" versions of previously approved drugs, to be further discussed below,[379] studies designed to determine whether the drug is more efficacious at the same amount of the active ingredient or whether there is a side effect reduction; (3) related to (2), studies showing that the new drug version meets the "change in safety, purity, or potency" standard used to compare so-called "biologic" products, also to be discussed further below;[380] (4) so-called "indirect comparisons" via analysis of clinical trial data gathered separately for the original and modified products that tend to establish some therapeutic distinction between the two;[381] (5) so-called "non-inferiority" trials that the FDA currently requires for approval of new anti-infective drugs;[382] (6) formal,

[376] *See, e.g.*, C. Peter N. Watson et al., *A qualitative systematic review of head-to-head randomized controlled trials of oral analgesics in neuropathic pain*, 15 PAIN RES. MANAGEMENT 147 (2010).
[377] *See* Kessler, *supra* note 71, at 438, 440.
[378] *See supra* notes 221-222 and accompanying text (discussing Seroquel XR).
[379] *See infra* notes 436-440 and accompanying text (discussing enantiomers).
[380] *See infra* notes 476-482 and accompanying text (discussing biologics).
[381] Schneeweiss et al., *supra* note 295, at 786 (describing indirect comparisons of data from separate placebo-controlled randomized clinical trials as a route for establishing comparative efficacy). Indeed, if the sponsor seeks to show a difference between two drug versions via an indirect comparison (or a non-inferiority study, *supra* note 382), the placebo-controlled approval data from the first product's approval can be used as the active control against which the approval data for the second product (likewise placebo-controlled) would be compared.
[382] *Non-Inferiority Clinical Trials to Establish Effectiveness: Guidance for Industry*, *supra* note 61. Note that, though only used for anti-infectives, this guidance provides a general rationale for using active controls: "Caregivers, third party payers, and some regulatory authorities have

randomized head-to-head clinical trials designed to assess relative safety and efficacy of the two drug forms;[383] (7) any other information the FDA deems relevant to the question of drug comparison, such as data on relative efficacy of the two versions in particular sub-populations. The labeling would make clear what specific study was done and describe its limitations.

B. The Promise of Clear Labeling, and a Further Potential Stick

1. Possible benefits of clear labeling

Will clear labeling make a difference? Whatever the potential advantages of labeling, it will certainly not get rid of the price disconnect or eliminate schemas and other cognitive limitations of the market participants.[384] In general, it is clear from many contexts that mandated disclosure is no panacea.[385] Still, the labeling can harness the ability of medical professionals to act more effectively as "learned intermediaries" on behalf of their patients by cutting through the noise generated by currently unchallenged advertising.[386] While mandated disclosure can fail "[w]hen simple data will not do the job, when considerable information is needed to make a good decision, and when experience is required to use information well,"[387] an insert that presents comparative study summaries in a user-friendly way—and is perhaps accompanied by above-mentioned education campaigns[388]—can go a long way toward nudging physicians toward sensible prescribing.[389] This dynamic can be

increasingly placed an emphasis on the comparative effectiveness of treatments, leading to more studies that compare two treatments," the guidance says. "Such studies can provide information about the clinical basis for comparative effectiveness claims, which may be helpful in assessing cost effectiveness of treatments. If a placebo group is included in addition to the active comparator, it becomes possible to judge whether the study could have distinguished treatments that differed substantially, e.g., active drug versus placebo." *Id.* at 7.

[383] *See supra* note 376 and accompanying text.

[384] *See supra* Part III.

[385] Omri Ben-Shahar & Carl E. Schneider, *The Failure of Mandated Disclosure*, 159 U. PA. L. REV. 647 (2011).

[386] *See* Russell G. Thornton, *The learned intermediary doctrine and its effects on prescribing physicians*, 16 BAYLOR U. MED. CTR. PROCEEDINGS 359 (2003). The role of the learned intermediary doctrine is to shield manufacturers from tort claims based on inadequate warnings. Underlying that the doctrine is the assumption that the prescriber is responsible for informing the patient of the risks and benefits of a drug. *But see* State v. Karl, 647 S.E.2d 899 (W. Va. 2007) (declining to adopt the doctrine in part because of the proliferation of direct-to-consumer advertising).

[387] Ben-Shahar & Schneider, *supra* note 385, at 746.

[388] *See supra* notes 345-347 and accompanying text.

[389] For skepticism, see Evans, *supra* note 60, at 508; *supra* note 348 and accompanying text. *See also* Darrow, *supra* note 49, at 368 ("Although drug labels are required to contain a section describing clinical trial results, this information is buried in section fourteen of the package

reinforced if professional norms help physicians build the instinct of "labeling first" when confronted with comparative advertising.[390] Finally, if nothing else, the labeling would provide a very clear signal for payers[391]—and the decisions of those payers inclined to make side deals with manufacturers to continue selling higher-priced drugs would at least be made more transparent,[392] perhaps leading to public pressure.

Indeed, the complete absence of comparative data in particular could be highlighted in a highly conspicuous manner, comparable to the "black box warning" one currently sees for particularly dangerous side effects of a drug.[393] And while the labeling would not directly resolve the hard switch problem, one imagines that an antitrust case against firms that product-hopped against the background of demonstrable absence of comparative data should be particularly straightforward to make out, resulting in the remedy of having both products on the market.[394] With the new information on the insert, moreover, physicians may be convinced to make the reverse switch more readily if that becomes necessary.[395] Therefore, the required labeling could ultimately help the market reward those sponsors who have made a credible case that the new version provides a therapeutic advantage or at least a useful distinction from the original. Conversely, sponsors who have failed to submit

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insert, is often written in such a way that it is difficult for doctors (let alone patients) to understand, and is not standardized even among drugs within the same category, making assessments of comparative efficacy difficult or impossible.") (citations omitted). Professor Darrow's characterization, however, refers to the current approach to labeling—which does not include comparative information and thus forces physicians who wish to engage in comparative analysis to piece together data from different drug inserts.

[390] *See generally* Ann Jacoby et al., *A qualitative study to explore influences on general practitioners' decisions to prescribe new drugs*, 53 BRITISH J. OF GEN. PRACTICE 120 (2003) (describing the role of norms in driving rational prescribing decisions).

[391] *Cf.* Liora Sukhatme, Note, *Deterring Fraud: Mandatory Disclosure and the FDA Drug Approval Process*, 82 N.Y.U. L. REV. 1210 (2007) (explaining the importance of disclosure of drug-related information for another class of individuals with financial stake in clinical trial data—investors); *see also supra* notes 283-289 and accompanying text (discussing the complex role of payers in drug pricing).

[392] *See supra* notes 290-292 and accompanying text.

[393] *A Guide to Drug Safety Terms at FDA* at 2, U.S. FOOD AND DRUG ADMIN. (Nov. 2012), https://www.fda.gov/downloads/forconsumers/consumerupdates/ucm107976.pdf. Although the patient does not normally see the package insert until after he or she acquires a drug from the pharmacy, and black box warnings are generally meant for clinicians as "learned intermediaries," not patients, the clinicians are required to discuss black box warnings with patients before prescribing the drug. *See* Becky Upham, *What is a Black Box Warning for a Drug?*, EVERYDAY HEALTH, https://www.everydayhealth.com/fda/what-black-box-warning-drug (last visited July 23, 2018). In a similar way, the proposed labeling might initiate a discussion of reasons for the switch from one form of the drug to another between the doctor and the patient.

[394] *See also infra* notes 509-512 and accompanying text (addressing this issue further).

[395] *Cf. supra* notes 20-21 and accompanying text (explaining that unwillingness to switch back to the generic could be driven by both patient welfare concerns and by the lack of advertising by generics).

relevant comparative data may fare less well in the now better-informed market for pharmaceutical drugs,[396] particularly when the new version is significantly more expensive due to patent protection. In sum, comparative 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."[397]

In addition to the immediate value of fostering more rational selections between alternative drug forms, the proposed approach—if it succeeds in eliciting a significant amount of comparative information between the versions—could have downstream benefits as well. Although pre-marketing data can be of more limited value than the real-world data actually developed after clinical practice begins,[398] there can be an important feedback mechanism between the two.[399] For example, pre-approval comparative efficacy studies on ADHD drugs in Europe have yielded important information that was supplemented in the course of clinical practice,[400] and this dynamic has been observed in other instances.[401] Thus, even when not definitive on the therapeutic effectiveness front, comparative studies performed by drug-makers before marketing can provide an impetus for future research and data analysis.[402] In all, by "motivating the provision of information"[403] in the drug-comparison scenario, the FDA could help drive medical and scientific innovation in the pharmaceutical space.

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[396] Holman et al., *supra* note 154 ("A critic of follow-on patents might argue that, even in cases in which the follow-on patent covers a trivial or illusory improvement, a drug company may promote the improved version and convince doctors to prescribe it in spite of it being more expensive than the original product and providing little, if any, additional benefit. If that were the case, it would not be the fault of the patent system; it would be a deficiency in the market that should be corrected.").

[397] Alexander & Stafford, *supra* note 58, at 2488; Sorenson et al., *supra* note 58; *see also* Bethany Fox, *Closing the Information Gap: Informing Better Medical Decisionmaking through the Use of Post-Market Safety and Comparative Effectiveness Information*, 67 FOOD & DRUG L.J. 83 (2012) ("The statutory efficacy requirements for approval do not require a determination of the relative effectiveness of the product as compared with other treatment options, which results in . . . dearth of premarket comparative information. Uncertainty regarding the risks and relative benefits of prescription drugs leaves physicians and patients in an information vacuum.").

[398] *See* Evans, *supra* note 60, at 470-74.

[399] *See supra* notes 293-300 and accompanying text.

[400] Bourgeois et al., *supra* note 300.

[401] Y.K. Loke & C.S. Kwok, *Dabigatran and rivaroxaban for prevention of venous thromboembolism–systematic review and adjusted indirect comparison*, 36 J. CLIN. PHARMACY & THERAPEUTICS 36, 111 (2011); Brett T. Venker et al., *Safety and Efficacy of New Anticoagulants for the Prevention of Venous Thromboembolism After Hip and Knee Arthroplasty: A Meta-Analysis*, 32 J. ARTHROPLASTY 645, 651 (2017); *see* Schneeweiss et al., *supra* note 295; van Lujin et al., *supra* note 331; *see also* Ijima, *supra* note 298.

[402] *See generally* Alexander & Stafford, *supra* note 58.

[403] Eisenberg, *supra* note 105, at 349, 373.

In particular, information generated under the proposed regime can contribute to the program of comparative effectiveness research (CER), which has become a significant national priority in the past decade. The statute that significantly broadened CER[404] and brought it into the national spotlight,[405] the American Recovery and Reinvestment Act of 2009, allocated 1.1 billion dollars toward research conducted in the two years since the statute's passage. A later statute, the well-known Affordable Care Act,[406] established "a permanent U.S. CER entity called the Patient-Centered Outcomes Research Institute [PCORI] . . . to guide the federal CER enterprise."[407] PCORI's mandate is comparative clinical effectiveness,[408] not cost-effectiveness, but Medicare administrators can consider its findings in coverage decisions.[409] Although the larger CER program, as administered through PCORI and elsewhere, is focused on post-marketing research, some commentators believe that a successful CER strategy requires production of "data prior to the widespread adoption of a drug or treatment" in order to be successful.[410]

Unsurprisingly, CER has generated controversy, with some commentators expressing concern that studies conducted under the aegis of the program would lead to rationing of care,[411] including denials of therapy options that are clinically justifiable but expensive. Although such critiques, while extremely weighty, are not insurmountable and have been addressed elsewhere,[412] it is important to reiterate that wide-ranging adoption of CER at the FDA is not the goal of this proposal.[413] The focus, instead, is strictly on follow-on versions of already-approved drugs

[404] Legislative efforts to install CER can be traced back to the 2003 Medicare Modernization Act, which created the first federal CER mandate. CAROL M. ASHTON & NELDA P. WRAY, COMPARATIVE EFFECTIVENESS RESEARCH xiii (2013).
[405] 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).
[406] Pub L. 111-148, 124 Stat. 119, 727-47, §§ 6301, 6302 (2010).
[407] Riaz Ali et al., *Comparative Effectiveness Research in the United States: A Catalyst for Innovation*, 4 AM. HEATH DRUG BENEFITS 68, 69 (2011).
[408] Saver, *supra* note 277, at 216.
[409] Ali et al., *supra* note 407, at 71.
[410] Alexander & Stafford, *supra* note 58, at 2488.
[411] *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.
[412] *See, e.g.*, Jerry Avorn, *Debate About Funding Comparative-Effectiveness Research*, 360 N. ENGL. J. MED. 1927 (2009).
[413] *Cf. supra* note 335 and accompanying text (discussing criticisms of proposals to make comparative efficacy a condition of approval).

coming from the same firm.[414] This emphasis is justified because the product-hop pattern has demonstrated particular susceptibility to information asymmetries and resulting market failures,[415] creating a need for mechanisms that could sort strategic conduct from genuine innovation.[416] Under this Article's proposal, the treatment options likely to be least favored are those for which the sponsor provided no comparison with the prior option at all, suggesting (price aside) that the patient might be unlikely to draw an incremental benefit from the change. Thus, the data developed under the proposal is unlikely to present ethically complex care rationing scenarios.[417]

2. The Orange Book *variation*

If the FDA's proposed authority for comparative data analysis and the corresponding addition to the labeling prove inadequate in eliciting such data, a more vigorous stick against product hopping is available. This measure concerns withholding the privilege of having a patent covering a drug product listed in the *Orange Book* from firms that fail to produce the evidence needed to meet the "relevant to relative performance" threshold. As discussed in Part I, the *Orange Book* provides an important linking mechanism between pharmaceutical patents and FDA approval.[418] 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."[419]

To recap the patent litigation consequences of an *Orange Book* listing, 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*

[414] *See* Ghislandi, *supra* note 173 (concluding that follow-on product changes take place "mainly between products of the same firm"); *see also supra* note 177 (noting that questions with respect to various corporate forms, such as subsidiaries and spinouts, would need to be addressed in the "same firm" inquiry).
[415] *See supra* Part III.
[416] Wertheimer & Santella, supra note 68, at 7 ("[I]t 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."); Joanna Shepherd, *The Prescription for Rising Drug Prices: Competition or Price Controls?*, 27 HEALTH MATRIX 315, 345 (2017) (addressing "sham innovation that does not justify shifts in marketing effort or redirecting consumers"); *see also* Mueller & Chisum, *supra* note 57, at 1106 n.12.
[417] *See generally* Govind Persad, *Priority-Setting, Cost-Effectiveness, and the Affordable Care Act*, 41 AM. J. L. MED. 119 (2015).
[418] *See supra* notes 110-115 and accompanying text.
[419] 21 U.S.C. § 355(b)(1) (2018).

Book-listed patents an act of patent infringement.[420] To seek approval of an ANDA when such patents exist, the generic firm must file a Paragraph IV certification with the FDA, setting forth the basis as to why each patent is invalid or not infringed.[421] Once the brand initiates the patent suit typically triggered by such a filing, FDA approval of the ANDA is postponed for 30 months unless all of the asserted *Orange Book* patents are adjudged to be invalid or not infringed before that time.[422]

The certification requirement and the 30-month stay of approval are significant regulatory benefits for brand companies that obtain approvals for their NDAs, and they are available for both pioneering and follow-on drugs.[423] To create a stronger form of inducement for comparative data generation, the FDA could, in addition to requiring the new labeling information, be given the discretion to exclude patents of sponsors who fail to provide relevant data from the *Orange Book*.[424] Although one way to implement the proposal is to deny a listing every time a firm fails to meet the proposed standard, a more flexible approach taking into account the particular circumstances of the switch could empower the FDA to use delisting more effectively as a deterrent.[425] Thus, the FDA's discretion to deny an *Orange Book* listing can be exercised in cases where the sponsor did not even attempt to surpass the threshold, or where the timing of the potential switch is particularly

[420] 35 U.S.C. § 271(e)(2) (2018).
[421] 21 U S C. § 355(j)(2)(A)(vii)(IV) (2018). A different statutory provision applies to "use" patents. *See id.* § 355(j)(2)(A)(viii).
[422] *Id.* § 355(j)(5)(B)(iii).
[423] *See generally* Bouchard et al., *supra* note 111; *see also* Dogan & Lemley, *supra* note 31, at 710-11.
[424] *Cf.* Eisenberg & Crane, *supra* note 34 (calling on the FDA to take on a greater role in managing *Orange Book* listings); Sherkow, *supra* note 34, at 214-15, 250-253 (similar). Nonetheless, unlike these proposals, this Article does not task the FDA with policing any aspect of substantive patent law—another area the agency has been unwilling to enter. Instead, the proposal goes to the FDA's core competency, which is the evaluation of safety and effectiveness of drugs.
[425] 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 those on pioneering forms of drugs, *id.* § 156(a)(5). *See* Ouellette, *supra* note 156, at 306 ("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)). Interestingly, though, patent extensions under this subsection have been allowed for so-called "prodrugs." *See* Photocure ASA v. Kappos, 603 F.3d 1372 (Fed. Cir. 2010); Ouellette, *supra* note 156, at 312 & n.84 (discussing this result). For further discussion of prodrugs, *see* Amy Kapczynski et al., *Polymorphs and Prodrugs and Salts (Oh My!): An Empirical Analysis of "Secondary" Pharmaceutical Patents*, 7 PLOS ONE e49470 (2012); *infra* note 439 and accompanying text.

suggestive of a strategic product hop.[426] The delisting authority would be a significant regulatory shift carrying with it the potential of reducing the incidence of such conduct—or, at the very least, encouraging the production of comparative data.

Even without an *Orange Book* listing, however, brand companies can sue generics for patent infringement once the latter launch the products under their ANDAs under traditional patent infringement theories (i.e., outside the Hatch-Waxman framework).[427] The generics would thus be exposed to the risks of monetary damages and potentially an injunction against further marketing of their products.[428] Nonetheless, at least approvals will not be delayed by Paragraph IV certifications and 30-month stays and, given that courts do invalidate follow-on patents with some frequency,[429] the risks may be worthwhile for the generics to take. In some cases, moreover, the FDA's determination of no therapeutic difference between the two products may be deployed to counter a theory of non-obviousness based on unexpected results, or at least as a route to questioning the data submitted by the sponsor in court.[430] 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, based on the deficient FDA submission[431]—favor

[426] Note that an exclusion of certain patents from the *Orange Book* does not violate the "anti-discrimination" provision of the AGREEMENT ON TRADE-RELATED ASPECTS OF INTELLECTUAL PROPERTY RIGHTS (TRIPS), Art. 27.1, an international treaty that the United States has acceded to, since *Orange Book* listings are viewed as a regulatory benefit that is not a part of the regular bundle of rights that comes with a patent. Indeed, some TRIPS jurisdictions do not have an *Orange Book* equivalent. *See generally* Bouchard, *supra* note 111.

[427] 35 U.S.C. § 271(a)-(c) (2018); *see* aaiPharma Inc. v. Thompson, 296 F.3d 227, 241 n.7 (4th Cir. 2002) ("It is important to recognize that the . . . patentee can still pursue patent infringement suits against generic manufacturers. It is simply deprived of the opportunity to litigate its infringement claims under the shelter of the thirty-month stay.").

[428] *See, e.g.*, AstraZeneca AB v. Apotex Corp., 782 F.3d 1324, 1330-32, 1344 (Fed. Cir. 2015).

[429] *See* Hemphill & Sampat, *supra* note 54.

[430] *Cf. supra* Part II.B.2 (explaining that evidence that has not been vetted by the FDA and lacks clinical validity can influence non-obviousness determinations at the PTO or during litigation); *see also* Jacob S. Sherkow, *Patent Law's Reproducibility Paradox*, 66 DUKE L.J. 845 (2017) (explaining that information developed after the filing of the patent sometimes brings to light the fact that the patent specification does not meet the enablement requirement of 35 U.S.C. § 112(a)).

[431] *See, e.g.*, Johnson & Johnson Vision Care, Inc. v. CIBA Vision Corp., 712 F. Supp. 2d 1285, 1290-93 (M.D. Fla. 2010) (denying an injunction in a health care patent infringement case based in part on the public interest factor for awarding injunction). Because of the proposed de-linking from the *Orange Book*, the patentee would not have a remedy of an automatic injunction against ANDA approval under 35 U.S.C. § 271(e)(4)(B), another important benefit of the listing. *See* Braintree Labs., Inc. v. Novel Labs., Inc., 749 F.3d 1349, 1367 (Fed. Cir. 2014) (Moore, J., dissenting) ("[W]hile the injunction remedy [under 35 U.S.C. § 283] rests within the discretion of the district court, the order to delay the approval of the ANDA until patent expiration is *not* discretionary. 35 U.S.C. § 271(e)(4)(A),(B). . . . [T]his is exactly what the statutory language commands. The statute requires the court to delay approval until expiration of the patent, even if

the defendant. And while the availability of monetary damages for infringement might discourage such "at risk" launches,[432] some generics might still be motivated to enter the market based on probability of invalidation. Moreover, while generic firms might balk at selling drug modifications for which the sponsor demonstrated no provable difference from the old form, the proposal should at least drive down the new form's prices. That, in turn, would encourage some generics to take a chance and challenge the brand.[433]

C. Categories of Qualifying Drug Changes

One critical task for the FDA under the proposed regime is to identify categories of drug changes that would be subject to the clear labeling requirement for dealing with potential product hops. While the determination is not straightforward one, it is encouraging that the FDA has already done some useful legwork by classifying New Drug Applications (NDAs) by product type. The different NDA product categories that the FDA recognizes include the "New Molecular Entity" category, which covers drugs having "an active ingredient that contains no active moiety that has been previously approved by the FDA" (Type 1); "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 "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

there is only a single infringement. And since the generic can't launch without FDA approval, the statute creates a de facto injunction.").

[432] *Cf. AstraZeneca*, 782 F.3d at 1344 (discussing measurement of the "value of what was taken" in the analysis of reasonable royalty damages in a Hatch-Waxman case). Another option for the prevailing patentee is the lost profits measure of damages. *See* David Manspeizer, *The Law on Damages in Generic Drug Launches Remains Vague* 2, N.Y. L.J. (Jan. 6, 2014), available at https://www.americanconference.com/blog/the-law-on-damages-in-generic-drug-launches-remains-vague (discussing complexities in this area of law).

[433] For further analysis, see Joseph M. O'Malley, Jr. et al., *Failure to launch*, INTELL. PROP. MAG. 30 (Apr. 2011).

that "contains a different strength of one or more active ingredients in a previously approved or marketed combination" (Type 5).[434]

Therefore, in spite of relying on the "safe and effective" standard demonstrable over a placebo for most new approvals and carefully noting "[t]hese codes are not indicative of the extent of innovation or therapeutic value that a particular drug represents,"[435] 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 and cannot be fairly classified as a new version of a known drug, the rest of the recited categories (e.g., Types 3 and 5, which should cover many extended-release drugs) are not and therefore provide an excellent starting point for an inclusive "product modification" class that would be subject to the proposed regime.

In addition to the categories identified by the FDA as Types 2 through 5, experience has taught of other recurring patterns of drug changes that may be made for strategic reasons. One contentious area includes a product change from so-called "racemate" drugs to pure "enantiomers," which—to simplify the chemistry significantly—entails taking a drug initially marketed as a mixture into two distinct, closely related molecules, separating the mixture into the individual components, and marketing one of them as a new drug.[436] In the context of deciding whether to grant a regulatory new chemical entity exclusivity, the FDA has struggled with classifying enantiomers, with Congress ultimately stepping in with a compromise solution of empowering the agency to grant exclusivity where the pure enantiomer is approved for new indications in a different therapeutic class.[437] The close chemical similarity between a racemate and one of its enantiomers, reinforced by decision-makers' unwillingness to treat purified enantiomers as full-on new chemical entities, suggests that such drug products should be treated

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[434] *FDA Manual of Policies and Procedures, NDA Classification Codes*, U.S. FOOD AND DRUG ADMIN., (Nov. 4, 2015), https://www.fda.gov/downloads/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cder/manualofpoliciesprocedures/ucm470773.pdf. The Manual also discusses two other types of new drug products that are not relevant to the purposes of this Article's proposal.

[435] *Id*. Conceptually similar to these categories might be chemical entities related to the original product, such as enantiomers and prodrugs, discussed below. *See infra* note 439; *see also supra* note 425.

[436] *See generally* Darrow, *supra* note 173; Kyle Faget, *Why FDCA Section 505(U) Should Not Concern us Greatly*, 15 MICH. TELECOMM. & TECH. L. REV. 453 (2009); *see also* Lemley, *supra* note 206, at 1377-39, 1384-86 (discussing the patenting of enantiomers).

[437] *See* 21 U.S.C. § 355(u) (2018); *see* Faget, *supra* note 436; Aparna Nemlekar et al., *FDA Is Evolving on Qualifications for "New Chemical Entity"*, PEPPER HAMILTON LLP, http://www.pepperlaw.com/publications/fda-is-evolving-on-qualifications-for-new-chemical-entity-2016-09-07 (Sept. 7, 2016).

as "modifications" of known drugs under this Article's proposal, triggering a comparative inquiry.

Moreover, as with extended-release formulations, the closest prior art to the enantiomer for patentability purposes is almost always its predecessor, the racemate, and unexpected results can play a similarly crucial role in the inquiry whether the enantiomer overcomes a § 103 hurdle.[438] The challenges of conducting this inquiry at the PTO and in court, raised throughout the Article, reinforce the conclusion that enantiomers should fall under the modification regime. As with other modifications, the FDA's power to examine the data critically would be a significant stick in this context.[439] To be sure, starting with the infamous

[438] *See, e.g.*, Aventis Pharma Deutschland GmbH v. Lupin, Ltd., 499 F.3d 1293, 1301-03 (Fed. Cir. 2007) (discussing unexpected clinical properties of the claimed enantiomer in the context of § 103 analysis); *see also* UCB, Inc. v. Accord Healthcare, Inc., 890 F.3d 1313, 1318 (Fed. Cir. 2018) (upholding validity of an enantiomer patent where the specification stated that "the R stereoisomer is unexpectedly more potent than the corresponding S stereoisomer and the racemic mixture") (citation omitted). To be sure, sometimes weighing against non-obviousness in enantiomer cases is the difficulty of the molecular separation—which, combined with unexpected properties, could bolster the case for patentability. *See, e.g.*, Sanofi-Synthelabo v. Apotex, Inc., 550 F.3d 1075, 1077-78 (Fed. Cir. 2008) ("The district court found that this separation was not a simple or routine procedure and that success in separation, as well as the allocation of properties, was unpredictable."); *see also* Forest Labs., Inc. v. Ivax Pharm., Inc., 501 F.3d 1263, 1269 (Fed. Cir. 2007); Mansfield, *supra* note 14. Conversely, the challenges of making the claimed formulation in a useful form are sometimes introduced to bolster non-obviousness of patents on extended-release formulations along with (or instead of) improved clinical properties. *See, e.g.*, Acorda Therapeutics, Inc. v. Roxane Labs., Inc., No. 14-882-LPS, 2017 WL 1199767, at *25 (D. Del. Mar. 31 2017) (noting an argument that the prior art compound "is highly soluble, making it difficult to slow its release"), *aff'd on other grounds*, Nos. 17-2078, 17-2134, 2018 WL 4288982 (Fed. Cir. Sept. 10, 2018).

[439] Another common modification type is the formation of a so-called "prodrug," a chemically modified version of the active drug that metabolizes to the active form of the drug. Such derivatives could improve therapeutic efficacy of the drug product, and also its stability. *See, e.g.*, Sherif I. Farag Badawy, *Effect of salt form on chemical stability of an ester prodrug of a glycoprotein IIb/IIIa receptor antagonist in solid dosage forms*, 223 INT'L J. PHARM. 81 (2001). Arguments made in this Article about new formulations and enantiomers apply to prodrugs (as well as other modifications such as new salt or crystalline forms of drugs), with the caveat that the discussion of manufacturing improvements in the paragraph that follows is also highly relevant to these products. *See, e.g.*, Millennium Pharm., Inc. v. Sandoz, Inc., 862 F.3d 1356, 1362, 1368-69 (Fed. Cir. 2017) (holding claimed ester prodrug held non-obvious, as established through "unexpectedly superior stability, solubility, and dissolution" where prior art compound was denied FDA approval because of instability); *cf. In re* Carabateas, 345 F.2d 1013, 1017-18 (C.C.P.A. 1965) (holding claimed ester prodrug obvious in spite of some improved therapeutic properties). Interestingly, the FDA already excludes metabolites—which can be thought of as a flip-side of prodrugs (as they are the active form of a drug into which the chemical ingested by patients metabolizes)—from the *Orange Book*. *See* 21 C.F.R. § 314.53(b) ("Process patents, patents claiming packaging, patents claiming metabolites, and patents claiming intermediates are not covered by this section, and information on these patents must not be submitted to FDA."); Sherkow, *supra* note 34, at 216, 252-53 (discussing this provision and using it as an example of *Orange Book* policing that the FDA does already). *Cf.* Schering Corp. v. Geneva Pharm., Inc., 339 F.3d 1373 (Fed. Cir. 2003) (discussing metabolites and invalidating a metabolite patent); *see also* Mueller & Chisum, *supra* note 57, at 1147-52 (using this case as an example of the Federal

example of thalidomide,[440] instances of enantiomers that offer significant clinical advantages over racemates abound,[441] and such advantages should be readily demonstrable in scenarios where they are actually present.

An interesting example of a drug modification type that may not involve a clinical benefit, but nonetheless could be a bona fide upgrade, is a change that improves the drug's manufacturing process, makes it easier to store the drug by increasing its shelf stability, and so on.[442] For these sorts of changes, 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 that shows improvements in handling and the like. Such information, though, does not traditionally go on the package insert (e.g., it is not a normal part of the labeling), and prescribers and patients are unlikely to care greatly about manufacturing changes in the clinical context anyway—unless, of course, the product is purer or somehow better for patients in other ways. Still, a clear "not proven different"-type notation may at least put the market participants, particularly payers, on notice that the change may be a strategic one.

In addition, it should be noted that some patents directed to manufacturing or handling improvements are not listable in the *Orange*

Circuit's efforts to combat evergreening). *But see* Holman et al., *supra* note 154, at 141-42 (providing example of a patented metabolite that provided a significant therapeutic advantage over the original drug).

[440] See Neil Vargesson, *Thalidomide-induced teratogenesis: History and mechanisms*, 105 BIRTH DEFECTS RES. (PART C) 140 (2015).

[441] *See, e.g.*, Auquier et al., *supra* note 15

[442] *See generally* W. Nicholson Price II, *Making Do in Making Drugs: Innovation Policy and Pharmaceutical Manufacturing*, 55 B.C. L. REV. 491 (2014). For a case law example in an argument for patentability was made based mainly on unexpected non-therapeutic properties of a new salt compound, though one discounted by the Federal Circuit, see Pfizer, Inc. v. Apotex, Inc. 480 F.3d 1348, 1368 (Fed. Cir.) ("[W]e hold that the optimization of the acid addition salt formulation for an active pharmaceutical ingredient would have been obvious where as here the acid addition salt formulation has no effect on the therapeutic effectiveness of the active ingredient and the prior art heavily suggests the particular anion used to form the salt."), *reh'g en banc denied*, 488 F.3d 1377 (Fed. Cir. 2007) (mem). *But see Pfizer*, 488 F.3d at 1382 ("[T]he panel improperly placed greater importance on the therapeutic value of a claimed compound over the value of its physical properties.") (Lourie, J., dissenting from denial of rehearing en banc); *id.* at 1384 ("The panel also mistakenly determined that the superior properties of the besylate did not overcome a prima facie case of obviousness because they showed no superior *therapeutic value*—the maleate salt form of amlodipine worked just as well as the besylate form in clinical trials. Therapeutic value, however, is just one property of a pharmaceutical. Other properties, such as solubility, stability, hygroscopicity, and processability, must also play a role in the analysis of advantages.") (emphasis added) (Rader, J., dissenting from denial of rehearing en banc); *cf.* Glaxo Grp. Ltd. v. Apotex, Inc., 376 F.3d 1339, 1343 (Fed. Cir. 2004) (successfully offering both surprising bioavailability and stability of an amorphous form of a compound as evidence of unexpected results over the prior art).

Book.[443] While this regulatory feature may limit the appeal of a product-hop strategy using this method, it also means that delisting would obviously not be a stick in the FDA's arsenal in these circumstances. Thus, to the extent that strategic product hopping based on purported manufacturing improvements is a concern, a different regime—perhaps one involving more vigorous antitrust enforcement—may be required.[444]

One category of inventions that should be exempted from the ambit of the proposal, however, are newly discovered methods of use of known compounds.[445] 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, patents on new methods of use of known compounds can be difficult to enforce effectively because merely manufacturing the drug is not an act of direct patent infringement[446]—so generics must be pursued under "indirect infringement" theories, which are more difficult to prove up.[447] The alternative, and a very impractical one, is to pursue prescribing physicians as direct infringers. Fourth, and finally, so-called "repurposing" or discovery of new indications of known chemicals has frequently led to highly significant health advances.[448] In all, there are reasons to believe that new use inventions are under-incentivized under the current regime, and more significantly they are not normally understood as "product hops." Thus, in the frame of this Article, a discovery of a new indication

[443] *See* 21 C.F.R. § 314.53(b) (2016) (excluding "[p]rocess patents, patents claiming packaging, patent claiming metabolites, and patents claiming intermediates" from *Orange Book* listings. Many drug modifications whose function could be to improve what are really a drug's manufacturing or handling features (e.g., shelf stability of the drug), such as crystalline (or polymorphic) forms, are listable, however. *See, e.g.*, Abbott Labs. v. Sandoz, Inc., 566 F.3d 1282, 1285-91 (Fed. Cir. 2009); *cf.* 21 C.F.R. § 314.53(b)(1)(2) (2016) (imposing unique test data requirements for *Orange Book* listings of polymorphs).

[444] *See supra* notes 17-25 and accompanying text.

[445] *See supra* note 141 and accompanying text.

[446] *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), available at https://www.bu.edu/law/files/2016/10/Solving-the-Problem-of-New-Uses-Ben-n.-Roin.pdf. *But cf.* Sam F. 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 incentives, such as patents and regulatory exclusivities).

[447] *See generally* Dmitry Karshtedt, *Causal Responsibility and Patent Infringement*, 70 VAND. L. REV. 565 (2017); Erika Lietzan, *Paper Promises for Drug Innovation*, 26 GEO. MASON L. REV. (forthcoming 2018), https://ssrn.com/abstract=3103293. *But cf., e.g.*, Sanofi v. Watson Labs. Inc., 875 F.3d 636 (Fed. Cir. 2017) (upholding a finding of indirect infringement by a generic manufacturer in a Hatch-Waxman case).

[448] *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).

would be a "per se" clinical advance that easily satisfies the proposed relevancy standard—though for ease of administration it should be excluded from the ambit of the proposal altogether.

D. Implementation Mechanics

The FDA has not asserted a general authority to request data tending to show a distinction between new and already approved drug products, in product-hopping cases or otherwise. Although FDA regulations allow sponsors to establish safety and efficacy of new drug products using active comparators, the agency has not attempted to make this method a general requirement for approval.[449] As suggested earlier, there are good reasons for this approach: If a drug product is determined to be safe and effective as a general matter, it seems extreme to deny the market an option to choose it altogether.[450] Moreover, considering the FDA's statutory mandate, a decision *not* to approve a product based on the fact that it is not proven to be therapeutically distinct from an existing product would present a conundrum for the agency. Because withholding of approval means that the product failed to meet the safety and efficacy thresholds,[451] such a decision would imply that the existing product, which is not demonstrably different from the one that has just been denied, is likewise not safe and effective and its approval should also be withdrawn.[452] This cannot be a sensible result.

Nevertheless, the FDA has used evidence of a significantly *improved* safety and efficacy profile of a new product to withdraw approval for a previous version.[453] The rationale in such cases is often that, given the availability of the newly approved option, the risk-benefit calculus now militates against leaving the old product on the market at all.[454] In addition, as the well-known example of opioid drugs lacking abuse-resistant forms illustrates, post-approval evidence concerning the

[449] *Cf., e.g.*, Sorenson et al., *supra* note 58 (suggesting making comparative efficacy a condition of drug approval in Europe).
[450] *Cf. supra* notes 335-338 and accompanying text (discussing these critiques).
[451] *See* 21 U.S.C. § 355(d).
[452] I thank Professor Patricia Zettler for suggesting that I make this point.
[453] *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."); Patricia J. Zettler et al., *Implementing a Public Health Perspective in FDA Drug Regulation*, 73 FOOD & DRUG L.J. 227, 228-39 (2018) (discussing this example); *see also* Holman et al., *supra* note 154, at 141-42 (providing another example).
[454] *See generally* Zettler et al., *supra* 453.

original product can sometimes come to light to justify its withdrawal further.[455] A perhaps cynical (though entirely plausible) take on this dynamic points out that companies have incentives to convince the FDA to pull an old product as part of a product-hopping strategy—an outcome that would prevent generics from marketing the prior version altogether.[456] While doing so without a good justification might amount to fraud—behavior that should be deterred by any number of legal regimes[457]—antitrust cases have revealed at least a milder version of this strategy, which is disparagement of one's prior product unaccompanied by an attempt to ask the FDA to withdraw approval.[458]

The proposed framework, to be clear, does not concern withdrawals of the old product based on insufficient safety or efficacy, but rather assumes that both versions are allowed to be marketed. To situate the proposal further, the scheme falls between the extremes of requiring comparative data for approval and the current approach under which the FDA does not typically perform any analysis of therapeutic distinctions between two drug products, even if they have the same active pharmaceutical ingredient. On what basis, then, can the FDA implement the proposal? Although the FDCA does not currently give the FDA clear authority to solicit comparative data between two drug products that meet the approval standard, history does show that the FDA has sometimes pushed the envelope on its statutory authority to pursue initiatives that it thought sensible. For example, confronted with widespread "off-label" use of drugs approved for adults in pediatric patients, the FDA in 1997 promulgated the so-called Pediatric Rule.[459] This rule, which the agency attempted to justify under various statutory anchors that included the FDCA's labeling provisions, imposed certain clinical study requirements with respect to a drug's pediatric uses even where the sponsor had not sought an approval for any pediatric indication for the drug.[460]

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[455] *Id.* at 237.

[456] Lars Noah, *Product Hopping 2.0: Getting the FDA to Yank Your Original License Beats Stacking Patents*, 19 MARQ. INTELL. PROP. L. REV. 161 (2015).

[457] *Cf.* Darrow, *supra* note 49, at 410-17 (describing the limits of fraud actions implicating FDA approvals); *see also* note 494 and accompanying text.

[458] *See, e.g. In re* Suboxone (Buprenorphine Hydrochloride and Naloxone) Antitrust Litig., 64 F. Supp. 3d 665, 682 (E.D. Pa. 2014). For a discussion of antitrust theories based on disparagement, see Michael A. Carrier & Carl J. Minniti III, *Biologics: The New Antitrust Frontier*, 2018 U. ILL. L. REV. 1, 60-64.

[459] *See generally* Michael S. Labson, *Pediatric Priorities: Legislative and Regulatory Initiatives to Expand Research on the Use of Medicines in Pediatric Patients*, 6 J. HEALTH CARE L. & POL'Y 34 (2002). I thank Professor Erika Lietzan for suggesting this example.

[460] *See* Ass'n of Am. Physicians & Surgeons, Inc. v. Food and Drug Admin., 226 F. Supp. 2d 204, 222 (D.D.C. 2002), *appeal dismissed on stipulation*, Nos. 02-5407, 03-5005, 2003 WL 22972071 (D.C. Cir. Dec. 11, 2003). Prior to the dismissal, the Court of Appeals for the District of Columbia

Although a district court struck down the Pediatric Rule as in excess of the FDA's statutory authority,[461] Congress later codified certain features of the rule.[462] This story is not unique: other initiatives, such as the so-called Priority Review of "applications for drugs that, if approved, would be significant improvements in the safety or effectiveness of the treatment, diagnosis, or prevention of serious conditions when compared to standard applications,"[463] were regulatory in origin but eventually garnered congressional ratification.[464] While I do not wish to advocate for lawless regulatory action,[465] one could argue nonetheless that it is not entirely inappropriate for an agency to test out a policy that has a plausible basis in the enabling statute, and may draw a response from stakeholders that is positive enough to lead to codification.[466] Taking a page from its pre-statutory Pediatric Rule playbook, the FDA could argue that "adequate directions for use"[467] must, in the product-hopping context, some information on what the switch would offer to patients or a

ordered the parties to "address in their briefs the question how this court can enforce a rule that the agency has not sought to defend on appeal and that the governing statute does not compel." Ass'n of Am. Physicians & Surgeons, Inc. v. Food and Drug Admin., Nos. 02-5407, 03-5005, 2003 WL 21384604 (D.C. Cir. May 28, 2003).

[461] *See id.* 211-22 (holding that the Pediatric Rule lacks a source of support in any of the provisions of the FDCA argued by the FDA, and is therefore beyond the agency's jurisdiction).

[462] *See* Pub. L. 108-155, 117 Stat. 1936 (Dec. 3, 2003).

[463] *Priority Review*, CTR. FOR DRUG EVALUATION AND RES., 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. REP. 15 (2015).

[464] *See* Kepplinger, *supra* note 463, at 24-25; *see also* Eagle Pharm., Inc. v. Azar, Civ. No. 16-790, 2018 U.S. Dist. LEXIS 101735 (D.D.C. June 8, 2018) (striking down a regulation that imposed the "clinically superior" standard for orphan drug approvals while acknowledging that Congress later passed a statute codifying this standard); *appeal docketed*, No. 18-5254 (D.C. Cir. Aug. 24, 2018); Depomed, Inc. v. U.S. Dep't of Health & Human Servs., 66 F. Supp. 3d 217, 226 (D.D.C. 2014).

[465] For a critical review of the FDA's tendency to push the boundaries of its authority, see Lars Noah, *Administrative Arm-Twisting in the Shadow of Congressional Delegations of Authority*, 1997 WIS. L. REV. 873.

[466] As noted, the FDA has imposed specialized approval requirements (e.g., a showing of efficacy relative to an active comparator rather than placebo) for some drugs in spite of the general language of the enabling statute. *See, e.g.*, *Non-Inferiority Clinical Trials to Establish Effectiveness: Guidance for Industry*, *supra* note 61; *see also Non-Inferiority Clinical Trials to Establish Effectiveness: Guidance for Industry*; *Availability*, 81 Fed. Reg. 78,605 (Nov. 8, 2016); *Draft Guidance for Industry on Non-Inferiority Clinical Trials; Availability*, 75 Fed. Reg. 9228 (Mar. 1, 2010). It is not clear how specifically the FDA has reconciled this guidance with the language of the statute, but it does not seem to have encountered significant opposition from the industry. *See, e.g.*, Comments of Pfizer, Inc., *Draft Guidance for Industry on Non-Inferiority Clinical Trials; Availability*, Docket FDA-2010-D-0075-0019 (June 1, 2010), https://www.regulations.gov/document?D=FDA-2010-D-0075-0019 (providing suggestions for improving the Guidance).

[467] 21 U.S.C. § 352(f)(1) (2018); *cf.* Ass'n of Am. Physicians & Surgeons, Inc. v. Food and Drug Admin., 226 F. Supp. 2d 204, 213-14 (D.D.C. 2002). The counterargument is that the sponsor is not seeking an indication for a comparative utility between two drug forms, however.

statement that no distinction has been demonstrated. Notably, while the decision striking down the Pediatric Rule took a particular issue with the fact that the Pediatric Rule *required* particular studies,[468] no such mandate inheres in this Article's proposal.

An amendment to the FDCA would, of course, be a legally surefire—though a politically much more difficult—route to the proposal's implementation. Moreover, the variation of the proposal vesting the FDA with the discretion to deny *Orange Book* listings to certain patents might be particularly prone to opposition (and, at the same time, less likely to find support in the current enabling statute).[469] But to the extent that one roadblock might entail questions about the FDA's experience with evaluating data purporting to show differences between drug products,[470] the amendment's proponents could point to numerous examples of the FDA's exercise of such authority. The aforementioned Priority Review program is one example.[471] Another is the FDA's requirement of non-inferiority trials for approvals of certain classes of drugs, such as antibiotics. As the term suggests, such studies are designed to show that the proposed drug is at least no worse than some option that is already on the market.[472] Moreover, the FDA applies comparative

[468] *Ass'n of Am. Physicians & Surgeons*, 226 F. Supp. 2d at 221.

[469] *See* 21 U.S.C. § 355(b)(1) (referring to listing requirement for "any patent which claims the drug for which the applicant submitted the application"). *But see* 21 C.F.R. § 314.53(b)(1) (excluding metabolites from *Orange Book* listings); *see also id.* § 314.53(b)(1),(2) (requiring special test data for "patents that claim only a polymorph").

[470] Indeed, even without a general requirement of comparative efficacy, such data is available as part of some approval packages—which means that the FDA sometimes analyzes data developed with the active comparator control. *See* Goldberg et al., *supra* note 295, at 1788 ("[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."). To be clear, the data set discussed in this study is for new molecular entity drugs. *See also* Downing et al., *supra* note 62, at 373-74 ("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."); Gottlieb, *supra* note 335, at 5 ("[D]rug companies already take on the enormous investment in preapproval superiority trials to gain market access for their new drugs. . . . In cases where drug makers undertake comparative trials to help secure reimbursement, they are doing the studies before approval and submitting them as part of their FDA files so they have the information available at the time of approval."). Nonetheless, it is clear that drug companies do not generate this information in a significant number of product hopping cases, perhaps in part because of the market failures discussed in Part III. *See supra* note 295 and accompanying text. In addition, there may be concerns with the quality and independent scrutiny of the voluntarily generated information. *See supra* note 296 and accompanying text.

[471] *See supra* notes 463-464 and accompanying text.

[472] *See Non-Inferiority Clinical Trials to Establish Effectiveness: Guidance for Industry*, *supra* note 61; *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-

standards in several other contexts involving small molecules, including the "clinically superior" standard under the Orphan Drug Act[473] and the "meaningful therapeutic benefit" standard under the Pediatric Research Equity Act.[474] Finally, the FDA's regulations explicitly contemplate approvals based on active comparator as a control.[475] These precedents can serve as platforms on which the FDA can build in further developing its product comparison expertise.

Still another example of the FDA's product comparison authority is worth highlighting. The provision of interest appears in the Biologics Price Competition and Innovation Act (BPCIA), the statutory framework that roughly parallels the Hatch-Waxman scheme for small molecules but in the context of biologics,[476] or large-molecule drugs.[477] Like Hatch-Waxman, the BPCIA is concerned in part with both rewarding innovation and enabling competition by new entrants, who could market so-called "biosimilar" drugs without having to conduct extensive clinical trials that the brand must perform to earn a pioneering drug's approval.[478] When a sponsor of a biologic product applies for a regulatory exclusivity to support a variation of a prior product that the sponsor is already marketing, the FDA must determine whether the structural change "result[s] in a change in safety, purity, or potency" relative to the

Focus/News/2016/11/07/26134/When-can-Non-Inferiority-Trials-Establish-Efficacy-FDA-Explains-With-Guidance. *But cf.* Gottlieb, *supra* note 335, at 3-5 (describing potential challenges with non-inferiority trials and some approaches to dealing with them). For another helpful discussion of non-inferiority trials, see Sandeep K. Gupta, *Non-inferiority clinical trials: Practical issues and current regulatory perspective*, 43 INDIAN J. PHARMACOLOGY 371 (2011).

[473] 21 U.S.C. § 360cc(c),(e).

[474] Pub. L. 108-155, 117 Stat. 1936, § 2(c) (2003) ("(1) if approved, the drug or biological product would represent a significant improvement in the treatment, diagnosis, or prevention of a disease, compared with marketed products adequately labeled for that use in the relevant pediatric population; or (2) the drug or biological product is in a class of products or for an indication for which there is a need for additional options."); *see also* Labson, *supra* note 459, at 54 (explaining that "[i]mprovement over existing products" under the "meaningful therapeutic benefit" standard for waiver of pediatric trials under the Pediatric Rule "would be demonstrated by 1) evidence of increased effectiveness in treatment, prevention, or diagnosis of disease, 2) elimination or substantial reduction of a treatment-limiting drug reaction, 3) documented enhancement of patient compliance, or 4) evidence of safety and effectiveness in a new subpopulation.").

[475] *See* 21 C.F.R. § 314.126(b)(2)(iv) (2018); *see also supra* note 470 and accompanying text.

[476] The parallels are, to be sure, rough—there are many significant differences between the Hatch-Waxman to the BPCIA, ranging from the length of the regulatory exclusivity period to which brands are entitled to the conduct of patent litigation between brands and biosimilar applicants. *See, e.g.*, Heled, *supra* note 87. *See generally* Krista Hessler Carver et al., *An Unofficial Legislative History of the Biologics Price Competition and Innovation Act of 2009*, 65 FOOD & DRUG L.J. 671 (2010).

[477] *See, e.g.*, Karshtedt, *supra* note 165, at 136-37; Bryan A. Liang, *Regulating Follow-on Biologics*, 44 HARV. J. ON LEGIS. 363, 369 (2007).

[478] *See generally* Carver et al., *supra* note 476.

predecessor product.[479] In a guidance for interpreting this subsection, the FDA explained that "[i]f the modified product affects the same molecular target as the previously licensed product, its sponsor should provide data to show that the changes in structure result in a change in safety, purity, or potency of the modified product when compared to the previously licensed product."[480] Similar to this Article's proposal,[481] this provision empowers the FDA to scrutinize differences between related products developed by the same firm, and has been characterized by several commentators as a deterrent against strategic product changes.[482]

Thus, the FDA must already compare drug products under various standards, and does so in several instances with Congress's explicit imprimatur. In addition to demonstrating the agency's expertise with such matters, the experience that the agency has developed in performing comparative analyses should be translatable to the setting of this Article's

[479] 42 U.S.C. § 262(k)(7)(C)(ii)(II) (2018). 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).

[480] *Guidance for Industry: Reference Product Exclusivity for Biological Products Filed Under Section 351(a) of the PHS Act* (Aug. 2014), https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM407844.pdf; *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 this guidance).

[481] *Cf.* Erika Lietzan, *The Uncharted Waters of Competition and Innovation in Biological Medicines*, 44 FLA. ST. U. L. REV. 883, 938-41 (2017) (criticizing this aspect of the BPCIA).

[482] *See* 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."); *id.* at 11 n.7 (stating that "the BPCIA contains anti-evergreening provisions intended to curb some of the strategic patenting seen in generic drugs"); 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 ("§ 351(k)(7)(C) is intended to prevent evergreening by excluding most product changes from qualifying for a new 12-year exclusivity period."); Heled, *supra* note 87, at 463-64 ("BPCIA accounts for the risk of abuse of statutory exclusivities by specifically and explicitly disallowing grants of market and data exclusivities under certain circumstances. . . . Patent law, on the other hand, does not seem to have the same kind of safeguards against abuse."). *See* Carver et al., *supra* note 476, at 764-66, 791-94 (2010) (discussing the BPCIA evergreening debate). As noted *supra* at note 67, "evergreening" is a term (often thought of as pejorative) that refers generally to strategies that brand companies use to maintain exclusivities for their products. *See, e.g.*, Robin Feldman, *May Your Drug Price Be Ever Green*, UC Hasting Res. Paper No. 256, available at https://ssrn.com/abstract=3061567; *see also* Prajapati & Dureja, *supra* note 214; Song & Han, *supra* note 101; Valoir, *supra* note 46. For overview of evergreening in a small-molecule context, see generally THOMAS, *supra* note 67.

proposal. Perhaps more to the point, Congress has already recognized the reality of product hopping, though only in the context of biologics. The proposal described here, then, adopts a related approach for small-molecule drugs.

V. OBJECTIONS

This Part briefly considers some anticipated objections to the proposal, including both that it goes too far and not far enough. Potential concerns are that the scheme set forth in this Article would diminish incentives for pharmaceutical innovation, would be avoided by sponsors or easily gamed, or would overwhelm the FDA in various ways. I address these objections in turn in the paragraphs that follow.

The first set of objections is rooted in the worry that the proposal would discourage cumulative pharmaceutical innovation, or even drug development generally.[483] It may be argued that, faced with the Hobson's choice of generating costly data or becoming subject to the scarlet letter of "not proven different," pharmaceutical companies would just opt out of the drug modification business altogether. This result would be a loss for human health, as it has been observed that some of the most effective drug products on the market are "tweaks" of those that are already known.[484] A further objection is that, given the relatively abbreviated period of useful exclusivity that brand companies receive given the long approval times for pioneering drugs, brand pharmaceutical firms need the "secondary exclusivity" for hopped drugs to recoup their research and development outlays.[485]

Several responses are possible to these objections. Data can of course be costly to generate, but the proposed standard provides for some relatively inexpensive ways, such as indirect comparisons, by which firms can meet the "relevancy" threshold.[486] Accordingly, if the new version of the drug actually has something provably different to offer, sponsors could avoid the "not proven different" designation without financially crushing preapproval efforts. In addition, firms meeting the standard would receive a number of added benefits that should boost incentives for follow-on research. Thus, the FDA's imprimatur would

[483] [Cite]
[484] Indeed, Professor Benjamin Roin has argued that, because many incremental innovations in the pharmaceutical space are in fact unpatentable, we have seen underinvestment of research into drug products that have high potential to improve human health. *See* Roin, *supra* note 141.
[485] *See supra* notes 143-147 and accompanying text.
[486] *See supra* notes 376-383 and accompanying text.

enable vigorous advertising of a drug's comparative benefit over the prior version[487] (and perhaps a more surefire way to convince payers to cover the new one),[488] should likely shield the firm from facing antitrust liability in a case of a hard switch,[489] and, as the Seroquel case illustrates, comparative data developed in the process may even bolster the case for validity of the patents covering the improved drug.[490] As to the further objection, to the extent that maintenance of exclusivity through secondary patenting and product hopping is needed to provide an adequate effective length of protection for pioneering products,[491] the solution is to extend pioneering patent term to account for regulatory delay[492] rather than encourage strategic behavior of the sort observed with Namenda.[493]

A second set of objections concerns possibilities that firms would continue to develop drug modifications, but either refuse to opt into the scheme (i.e., by not developing any comparative data) or game it by demonstrating therapeutic distinctiveness based on some minor parameter.[494] To develop the former objection, one would maintain that, besides costs of information generation, there are other powerful disincentives for firms to perform comparative analysis between two of

[487] Thus, with the comparative information on the insert, drug firms could advertise the advantages of the drug to clinicians without the concern of facing a lawsuit for misbranding. *See supra* notes 307-308 & 373-374 and accompanying text.
[488] *Cf.* Gottlieb, *supra* note 335, at 5.
[489] *See supra* notes 331-332 and accompanying text.
[490] *See supra* notes 216-222 and accompanying text.
[491] *See supra* note 143 and accompanying text. Of course, although the product hop accompanied by secondary patenting can enable the manufacturer to maintain control over the market, the exclusivity is not really being extended because the primary patents have expired. *Cf.* Jonathan J. Darrow, *Debunking the Evergreening Patents Myth*, 131 HARV. L. RECORD 6 (2010).
[492] *See* Josh Bloom, *Should Patents on Pharmaceuticals Be Extended to Encourage Innovation?*, WALL ST. J. R4 (Jan. 23, 2012); *see also* Erika Lietzan, *The History and Political Economy of the Hatch-Waxman Amendments*, 49 SETON HALL L. REV. (forthcoming 2019), https://ssrn.com/abstract=3140141 (explaining that the purported compromise of the Hatch-Waxman Act was actually a bad deal for brand companies).
[493] *See supra* notes 17-25 and accompanying text.
[494] Commentators have expressed concern that sponsors' control of the relevant information might enable it to succeed before the FDA by manipulating clinical trial results. Maria Elena Flacco et al., *Head-to-head randomized trials are mostly industry sponsored and almost always favor the industry sponsor*, 68 J. CLIN. EPIDEMIOLOGY 811 (2015); *see also* Thomas O. McGarity, *Beyond* Buckman*: Wrongful Manipulation of the Regulatory Process in the Law of Torts*, 41 WASHBURN L.J. 549, 559 (2002) ("When the onus is on the regulatee to provide data establishing that its product is 'safe and effective' . . . , the temptation is strong for a company to discount data indicating that the product may not meet the statutory test."). Still, the advantage of this Article's proposal over what is done currently is that comparative claims might now go completely unvetted. As to the problem of firms' presentation of inaccurate information to the FDA, claims against pharmaceutical companies based on "fraud-on-the-FDA" theories have ended in mixed results. *See, e.g.*, Desiano v. Warner-Lambert & Co., 467 F.3d 85 (2d Cir. 2006) (allowing such claims under Michigan law), *aff'd by an equally divided court*, 552 U.S. 400 (2008) (mem.). *But see* Lofton v. McNeil Consumer & Specialty Pharm., 672 F.3d 372 (5th Cir. 2012) (disagreeing with the reasoning of *Desiano* and holding fraud-on-the-FDA claims preempted under Texas law).

their own products. One, gathering data involving an already-approved product could reveal information exposing the sponsor to tort liability,[495] to the extent the tort claims are not preempted by federal law or FDA regulations.[496] Two, comparative analysis might show that the new product is unquestionably inferior, putting the sponsor in a tough spot.[497] Three, although the fact that firms sometimes already compare their own products voluntarily suggests that concerns about unearthing negative information do not prevail in every case,[498] the objector would maintain that the extant proposal would not alter the general cost-benefit calculus in this industry.

To address these concerns, I note that the market could well view the very refusal to opt into the proposed scheme as a signal that something is wrong with its products—either old, new, or both. Given the relative permissiveness of the standard and, particularly in the case of the proposal's *Orange Book* variation, the significance of the benefit being withdrawn,[499] firms that fail to show meaningful differences between their products to the FDA would need to counteract the negative inferences likely to arise from their decisions. In order to do so, those firms may therefore still need to reveal some comparative information to other market participants. Although this route would sidestep the FDA's examination of the data, the ultimate result would still entail a transfer of potentially useful information, which is the overarching goal of the proposal. While there might be concerns about the quality or reliability of the information generated this way, the fact the sponsor had the "FDA-

[495] Cahoy, *supra* note 296, at 625-26 ("Because greater transparency generally means greater tort exposure, companies may make the logical choice to simply diminish the source of liability. In other words, companies may reduce the amount of information they create (e.g., by conducting fewer voluntary clinical trials."); Allan M. Joseph, *Kid Tested, FDA Approved: Examining Pediatric Drug Testing*, 72 FOOD & DRUG L.J. 543, 548 (2017) ("Manufacturers are often reluctant to perform additional trials of any sort after approval because such trials 'pose a risk of exposing previously unrecognized toxicities, thereby reducing rather than expanding product demand.'") (quoting Eisenberg, *supra* note 446, at 720).

[496] *See, e.g.*, Wyeth v. Levine, 555 U.S. 555 (2009); *see also* Jodie M. Gross & Judi Abbott Curry, *The Federal Preemption Debate in Pharmaceutical Labeling Product Liability Actions*, 43 TORT TR. & INSURANCE PRACTICE L.J. 35 (2007); *cf.* Catherine M. Sharkey, *Federalism Accountability: "Agency-Forcing" Measures*, 58 DUKE L.J. 2125 (2009) (discussing FDA's strategies for having required drug labeling preempt state law tort claims).

[497] Eisenberg & Price, *supra* note 299, at 18 ("[C]omparative effectiveness research runs the risk of showing that a new drug is worse than existing treatments. Since placebo-controlled trials are generally enough to win regulatory approval, drug companies may decide not to take the risk of demonstrating inferiority rather than superiority for the patent-protected product."); D.N. Lathyris et al., *Industry sponsorship and selection of comparators in randomized clinical trials*, 40 EUR. J. CLIN. INVEST. 40, 40 (2010).

[498] *See supra* notes 221-222 and accompanying text; *see also supra* note 470 and accompanying text.

[499] *See supra* notes 423-425 and accompanying text.

vetting" option and decided to forgo it should at least lead payers, prescribers, and patients to discount it accordingly.

As to the "gaming" part of the objection, the relevancy standard is undoubtedly permissive, though one that is deliberately so given the major shift in the FDA's role proposed here and the concern that a more rigorous standard, such as clinical superiority, could have a severely negative impact on drug development. In any event, if one is proceeding from the assumption that pharmaceutical firms are prone to gaming the regulatory system, they are much more likely to escape consequences for such conduct if the only one government agency, the PTO, ever gets to rely on comparative data as a factor in setting the brand company's level of incentive.[500]

As noted throughout, the FDA has more experience with examining clinical trial data than the PTO, as well as the power to elicit information from sponsors beyond that which is submitted initially.[501] Moreover, the FDA has the necessary expertise to examine the data and work with the sponsor to limit the comparative claim to what the evidence actually supports.[502] The FDA's involvement ensures that, if the firm conducted the bare minimum of experimentation to meet the proposed threshold of "data relevant to relative performance of new product versions," then market participants would be informed that that was the extent of analytical work that the sponsor did.

Significantly, an approach that seeks to characterize precisely the nature of the claimed therapeutic improvement (or distinction) differentiates this Article's proposal from what is done at the PTO, which is an all-or-nothing decision on patentability. And while the PTO has a role to play in tailoring the brand's right by determining the permissible scope of the patent claim in view of the prior art and other requirements of the Patent Act, the Namenda XR example shows that (putative) patentability does not always correspond to any actual benefit offered by the modification.[503] Thus, while the standard could be gamed—and, if the result is to maintain *Orange Book* listings, the payoff of such a strategy would be significant[504]—the proposal would still succeed in at least eliciting some relevant information on what the drug change would offer.

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[500] *See supra* notes 258-261 and accompanying text.
[501] *See supra* notes 361-369 and accompanying text.
[502] *See supra* note 296 and accompanying text.
[503] *See supra* Part II.B.2 and accompanying text. I say "putative" because the validity of the Namenda XR patent has not yet been fully tested post-issuance.
[504] *See supra* notes 423-425 and accompanying text.

Third, the objector could raise the FDA's various institutional limitations as potential roadblocks to this proposal's successful implementation. For example, even if the FDA has the technical expertise to conduct the necessary analysis, it might not have the budget or the time to do it properly.[505] Combining those concerns with the agency's well-known aversion to risk,[506] perhaps the FDA would conclude as a matter of course that no relevant difference was established. And if the answer to the budgetary concern is to fund the initiative through user fees,[507] perhaps the FDA would then become captured and tilt toward the sponsors, issuing determinations that portray the modifications in an unduly favorable light.[508] Finally, the objector would note that even with its newfound power to elicit comparative information, the FDA cannot do anything about hard switches.[509]

Such objections are valid, but not insurmountable. Although it is true that the new authority would increase pressures on the FDA's resources, some of the added expense could be covered by outlays from the funds budgeted for CER.[510] The use of CER funding could be defended because pre-approval comparative analysis can dovetail with the CER conducted after the drug is marketed, driving 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 (i.e., placebo-based) drug approval,

[505] *See, e.g.*, Ron Nixon, *Funding Gap Hinders Law for Ensuring Food Safety*, N.Y. TIMES (Apr. 7, 2015), https://www.nytimes.com/2015/04/08/us/food-safety-laws-funding-is-far-below-estimated-requirement.html.

[506] *See, e.g.* Epstein, *supra* note 333, at 12 ("The harms that are caused by particular therapeutic agents—such as thalidomide, which causes major limb deformities—attract immense political pressures to ban these dangerous products from the marketplace. Overall, the result is a strong bias to overweigh Type I error [of erroneous approval] relative to the quiet harms that arise when individuals die for want of therapeutic agents that languish unapproved within the FDA.").

[507] *See* Prescription Drug User Fee Act, Pub. L. 102-571, 106 Stat. 4491 (Oct. 29, 1992).

[508] *See, e.g.*, Cahoy, *supra* note 296, at 670 ("[T]he [Institute of Medicine] Report noted that the agency's heavy reliance on user-fees for funding exacerbates the concern regarding industry influence.") (citing *Institute of Medicine of the National Academies, The Future of Drug Safety: Promoting and Protecting the Health of the Public* 73 (2007)); *see also* Dogan & Lemley, *supra* note 31, at 689-90, 699; James T. O'Reilly, *Losing Deference in the FDA's Second Century: Judicial Review, Politics, and a Diminished Legacy of Expertise*, 93 CORNELL L. REV. 939 (2008) (providing examples of the FDA's political capture). *But cf.* Rachel E. Barkow, *Insulating Agencies: Avoiding Capture Through Institutional Design*, 89 TEX. L. REV. 15 (2010) (proposing various mechanisms for shielding agencies from undue influence); *see also id.* at 47 & n.178 (contending that "the FDA is relatively more independent than other executive agencies, with its heads often advocating for drug regulation regardless of the position of their appointing president[,]" but noting concerns with capture) (citations omitted).

[509] *See supra* notes 393-394 and accompanying text.

[510] *See supra* notes 404-410 and accompanying text.

creating economies of scale for the agency. Finally, risk-averseness might not be a barrier to correct decision-making by the FDA here because proposed determinations do not come with the same kind of pressure as the decision whether the product actually goes on the market.

As for hard switches, the FDA certainly has little power to stop them—if a company voluntarily decides to discontinue an approved product, it is not clear if the agency could do anything to keep it on the market. As noted earlier, withholding product approval based on the lack of demonstrable difference from an already approved product is not a viable strategy given the FDA's enabling statute, nor is it likely to be sound policy.[511] While antitrust actions remain as a weapon against hard switches with no demonstrated difference,[512] the major concern here again comes down to gaming. Firms might do just enough to get over the relevancy hump—perhaps enabling them to avoid an antitrust action based on a procompetitive justification—and then pull the original product prior to the expiration of the pioneering patents. Even if the FDA's involvement fixes the information gap, physicians would have no choice but to switch if there is no original product. Whether, after those patents do expire, a switch back is plausible is an open question to which the answer depends on specific circumstances, including the nature of the condition being treated, patient characteristics, and the therapeutic difference between the drugs that has been established by the sponsor. At the very least, though, market participants should have a much better sense than before of the costs and benefits of this step—one of the goals of the proposal. And, in contrast to what happened with Namenda, one might actually see switches to drug products that are provably different, and perhaps better, than the original.

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

[511] *See supra* notes 449-452 and accompanying text.

[512] *Cf.* Dogan & Lemley, at 711-17 (providing a framework for antitrust analysis of this conduct); *see also* 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*, *supra* note 80, https://www.regulations.gov/document?D=FDA-2017-N-3615-0064 (suggesting that the FDA refer apparently problematic product hops to the Federal Trade Commission).

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 on advancing the quality of patient care and human health.[513] 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.

[513] Professors Yaniv Heled, Liza Vertinsky, and Cassady Brewer have recently made a proposal for a fundamental change along these lines. They argue "that companies involved in the provision of healthcare products and services should be incentivized or even required to assume alternative business forms that would both enable and require them to consider the needs of a broader range of stakeholders and the public interest in addition to shareholder value." Yaniv Heled et al., *Why Healthcare Companies Should Be(come) Benefit Corporations*, 60 B.C. L. REV. (forthcoming 2019), https://ssrn.com/abstract=3179622.