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Erika Lietzan

University of Missouri School of Law, lietzane@missouri.edu

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Recommended Citation

Erika Lietzan, Paper Promises for Drug Innovation, 26 *George Mason Law Review* 168 (2018).

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PAPER PROMISES FOR DRUG INNOVATION

*Erika Lietzan**

INTRODUCTION

Innovation does not stop when new medicines are launched. Companies with approved drugs and biologics continue to study their products for years after the initial approval—for instance, exploring new ways to formulate their drugs or modifying the active ingredients to introduce versions with different, and sometimes better, safety and effectiveness profiles. They also routinely study their products for usefulness in treating new conditions. This continued research requires time and money, and companies will not invest that time and money without adequate reason to do so. This Article examines the incentives federal law provides for new-use research, concluding that current incentives are little more than paper promises.

U.S. law provides two primary incentives for companies to study new uses of approved medicines: patent protection and regulatory exclusivity.¹ As

* Associate Professor of Law, University of Missouri School of Law. I am grateful for comments from Bruce Artim, Richard Epstein, Betsy Flanagan, Dmitri Karshtedt, David Korn, Neal Parker, Nicholson Price, and Jon Santamauro. I am also grateful for comments from audience members and fellow panelists at two conferences where this Article was presented—*Real Intellectual Property Reform*, Center for the Protection of Intellectual Property, Scalia Law School (Oct. 12–13, 2017), and *Clinical Innovation: Fair and Effective Incentives for New Uses of Established Drugs*, University College London and Georgetown University Law Center (Feb 8–9, 2018)—including Robert Armitage, Becky Eisenberg, and Kurt Karst. Finally, I am grateful for the research assistance of James Kopfensteiner (University of Missouri School of Law, Class of 2018) and for research grants from Shook, Hardy & Bacon and the Hulston Faculty Research Fellowship in Healthcare Law.

¹ Various other aspects of state and federal law might, in some capacity ancillary to their primary function, encourage companies to study new uses (for instance, as a condition of insurance coverage). See *infra* note 52. This Article focuses on new-use patents and regulatory exclusivity, however, which are *designed* to encourage new-use research. It uses the phrase “regulatory exclusivity” to refer to exclusivities administered by FDA. The phrase is not meant to imply that the exclusivities are regulatory inventions. They are not; they appear in federal statute. See, e.g., Drug Price Competition and Patent Term Restoration Act, 98 Stat. 1585 (1984). Regulatory exclusivities include five-year exclusivity for new chemical entities, three-year exclusivity for new drug products and new (drug) conditions of use, and twelve-year exclusivity for biological products. *Patents and Exclusivity*, FDA/CDER SBIA CHRONICLES (CDER Small Bus. and Industry Assistance Division, Silver Spring, MD), May 19, 2015, at 2; Erika Lietzan, *The Myths of Data Exclusivity*, 20 LEWIS & CLARK L. REV. 91, 93 (2016) (noting the twelve-year period for biological products). These are also known as “data exclusivity” or “data protection,” because they prevent a company’s competitor from relying in its own application on the data that supported the approval in question. See Lietzan, *supra*, at 107 (describing data exclusivity as a period before the time when competitors can gain a license from another’s previous research). Regulatory exclusivity also

a general rule, patents and regulatory exclusivity are designed to operate as temporary barriers to entry, allowing the beneficiary to enjoy an exclusive position in the marketplace.² The attendant profits operate as the incentive to conduct the research in question, and society accepts the short-term pricing consequences of exclusivity because it deems the research beneficial.³

At the same time, U.S. law is designed in part to ensure prompt approval of lower cost generic drugs when patents and exclusivity protecting the active ingredient and initial use of a medicine expire and to facilitate automatic substitution of those generic drugs when physicians prescribe the corresponding brand products.⁴ In connection with the approval, distribution, and use of generic drugs, however, Food and Drug Administration (“FDA”) practices and policies, state laws and policies, and healthcare professional and payer behaviors undercut the patents and exclusivity protecting new uses.⁵ In fact, generic drugs are routinely and knowingly dispensed for “infringing uses,” defined in this Article to mean uses covered by another company’s patent or regulatory exclusivity.⁶ Moreover, it is nearly impossible under current law for innovators to enforce their rights.

This must stop. It turns the incentives to develop new uses into nothing more than paper promises. As this Article explains, the practices and policies that give rise to this problematic dispensing are not *necessary* to ensure prompt approval and rapid uptake of generic drugs for non-infringing uses. And there is no excuse for a system that is clumsy and over-inclusive, resulting in sales and uses that are indisputably inconsistent with the objectives of federal law.

Legal, economic, and health policy scholars have grappled for years with what Professor Eisenberg once dubbed the “new-use problem”—the challenge of encouraging new-use innovation in the face of a broader healthcare system (meaning the system that governs approval, prescribing, dispensing, and paying for medicines) that effectively ignores new-use

includes seven-year orphan exclusivity, which is better understood as a type of “market exclusivity,” because it precludes approval of competing drugs even when supported by original data. *See id.* at 110–11.

² *See infra* Part II. The beneficiary may still face competition in the marketplace, in the form of competing products to treat the same condition.

³ There is a vast literature, beyond the scope of this Article, exploring the benefits and costs of patent protection from a utilitarian perspective. *E.g.*, Gregory Dolin, *Exclusivity Without Patents: The New Frontier of FDA Regulation for Genetic Materials*, 98 IOWA L. REV 1399, 1423 (2013) (“Patent law, then, must always maintain the uneasy balance between providing sufficient incentives to invent and disclose, which in the aggregate, promote further innovation, and guarding against granting overly broad patents, which retard further research and thus are detrimental to the common good.”).

⁴ *See* Erika Lietzan, *The Uncharted Waters of Competition and Innovation in Biological Medicines*, 44 FLA. ST. L. REV. 883, 888–89, 936–37 (2017).

⁵ *See infra* Part III.

⁶ This Article refers to these sales as “infringing sales” and the uses as “infringing uses,” although this is not meant to imply that the innovator has a cause of action against anyone in particular for the sale or use in question. In some cases, the innovator might—as when a use infringes a patent claiming the method of use. *See infra* Section III.B.

patents and exclusivity.⁷ This Article adds to the conversation, suggesting that there is nothing wrong with the patent and regulatory exclusivity incentives in themselves, aside from their being so easily circumvented, and that policymakers should focus on reforming the policies and practices in the healthcare system that lead to their circumvention.

Thus, FDA should revise its practices and policies that lead to automatic substitution of generic drugs for infringing uses, and the agency should enforce its existing rules and policies that would prevent generic companies from inducing this substitution. And policymakers should consider legislation to stimulate the key stakeholders (pharmacists, payers, and generic companies) to develop a system that will prevent infringing sales and uses. Left to their own devices but properly motivated, these stakeholders might turn to indication-based prescribing, dispensing, and pricing.

This Article claims that the new-use problem is *not* an inherent inadequacy of new-use patents or new-use exclusivity but, instead, a combination of policies and practices in the broader healthcare system that are not necessary to achieve cost-savings from appropriately dispensed generic drugs. Rather than enacting new intellectual property incentives or radically changing how medical research is funded, policymakers should take the more modest step of motivating stakeholders to develop a system that allows patents and exclusivity to have the effect Congress intended.

This Article proceeds as follows. Part I describes new-use innovation: how and why it occurs, and the value it brings. Part II describes the two primary incentives for new-use innovation provided by federal law: patents and regulatory exclusivity. Part III describes the rules, policies, and practices at FDA, in the states, and in the healthcare delivery and finance systems that effectively eviscerate new-use patents and exclusivity, and it explains why innovators are essentially unable to enforce their rights. Part IV describes the steps that FDA should take to correct its own rules, policies, and practices that contribute to the new-use problem. It also describes several legislative options for Congress that should motivate the key stakeholders to design a system that avoids infringing sales and uses, and it briefly responds to some of the primary objections these proposals would face.

The Conclusion describes some of the alternative solutions proposed for the new-use problem. This Article does not take a position in favor of any of the legislative options described in Part IV, which deserve more thorough

⁷ Rebecca S. Eisenberg, *The Problem of New Uses*, 5 YALE J. HEALTH POL'Y L. & ETHICS 717, 720 (2005) (concluding that patents, FDA regulations, and trade secrecy "offer[] firms some protection from free riders" but that "each has significant shortcomings as a regulatory mechanism for promoting the development of information about the effects of drugs"). This Article does not review the literature in the field, nor does it catalog the solutions offered by others. For an introduction to the scholarship on these issues, consider Professor Eisenberg's essay as well as Benjamin N. Roin, *Solving the Problem of New Uses* (Oct. 14, 2016) (unpublished manuscript) (on file with author) (noting numerous strategies to address the problem but ultimately focusing on use of information technology to provide pharmaceutical companies with information about indication-based prescribing and dispensing, so that they can set differential prices and enforce new-use patents).

vetting than is possible here. Instead, it claims that the relevant stakeholders could solve the problem of new uses if properly motivated. The Conclusion explains that policymakers should try this *type* of approach first, rather than a more fundamental change to how we encourage innovation.

I. DEVELOPMENT OF NEW USES

Approval of a new drug or biological product—collectively, here, “medicines” or “products”—requires a marketing application demonstrating the medicine in question is safe and effective when used as described in the labeling for prescribers.⁸ Developing the data necessary for approval of this application entails laboratory and animal (“preclinical”) studies followed by human (“clinical”) studies that usually proceed in phases from small trials examining how the body and drug interact to larger trials that prove safety and effectiveness.⁹ A typical program culminates in two randomized, controlled, double-blinded trials designed to test the product’s effectiveness for each medical use (also known as an “indication”) in its labeling.¹⁰ These final trials—also known as its “phase 3 trials”—are usually the most expensive part of a premarket research and development program.¹¹ At the end of this process, the manufacturer submits a marketing application describing the

⁸ Biological medicines and non-biological medicines reach the market pursuant to applications filed under different statutes. FDA “licenses” biologics under section 351 of the Public Health Service Act (“PHSA”), Pub. L. No. 78–410, 58 Stat. 682 (1944) (codified as amended at 42 U.S.C. § 262 (2012)). It “approves” non-biological “drugs” under section 505 of the Federal Food, Drug, and Cosmetic Act (“FDCA”), Pub. L. No. 75-717, 52 Stat. 1040 (1938) (codified as amended at 21 U.S.C. § 355 (2012)). This Article uses “medicines” to refer to both together, but “drug” or “biologic” when the distinction matters or when referring to a specific product.

⁹ FDA’s regulations describe three phases of clinical trials. Phase 1 trials are small trials, often in healthy volunteers, designed to generate safety information and information about how the body processes the drug. Phase 2 trials involve more subjects, often with the disease under investigation, and generates preliminary measurements of the drug’s effects on the body as well as information about optimal dosing. The process ends with phase 3 trials designed to test whether use of a particular finished product (which the company plans to commercialize) achieves a particular clinical endpoint in a specific population. *See* 21 C.F.R. § 312.21 (2017). These regulations describe the traditional approach, but in practice the modern approach is more varied. For example, a company might combine aspects of different phases in one trial (such as a “phase 1/2 trial”) or proceed seamlessly from one phase to the next. Regardless of the precise design of a clinical program, it proceeds in stages as more is learned about the compound, and it concludes with trials that demonstrate effectiveness for a particular use.

¹⁰ 21 U.S.C. § 355(d) (2012) (defining the “substantial evidence” standard for new drug approval); 21 C.F.R. § 314.126(b) (defining adequate and well-controlled investigations).

¹¹ In 2016, the average development costs for an approved drug were \$25.3 million for phase 1, \$58.6 million for phase 2, and \$255.4 million for phase 3. Joseph A. DiMasi et al., *Innovation in the Pharmaceutical Industry: New Estimates of R&D Costs*, 47 J. HEALTH ECON. 20, 24 (2016); *cf.* Institute of Medicine (IOM), *TRANSFORMING CLINICAL RESEARCH IN THE UNITED STATES: CHALLENGES AND OPPORTUNITIES* 3–4 (2010) (“Phase III clinical trials have become extraordinarily expensive.”).

product, how it is made, and the data generated during research and development.¹²

FDA approval of a new medicine means that the medicine's benefits outweigh its risks when it is used as described in the labeling, based on the data from this rigorous—yet inherently limited—premarket program.¹³ After approval, the company's understanding of the medicine's safety and effectiveness for the labeled uses becomes more refined, as the medicine is used by a broader population over a longer period of time than could be studied before approval.¹⁴

Companies typically also continue to invest in research and development.¹⁵ A company might seek to improve the clinical profile of its product, for instance, by developing a formulation or route of administration with a better safety profile (particularly if widespread clinical use has given rise to concerns that were not evident in the limited and controlled premarket trials) or improved effectiveness (perhaps by extending the drug's half-life in the body).¹⁶ Some incremental innovations can lead to therapeutic options for previously untreated subpopulations; for example, a new dosage form might be suitable for geriatric patients.¹⁷ Others might improve the convenience of the product; for example, an extended release formulation may reduce the frequency of dosing, which can improve patient compliance and in turn

¹² 21 C.F.R. § 314.50; 21 C.F.R. § 601.2.

¹³ 21 C.F.R. § 314.50(d)(5)(viii) (requiring new drug applications to discuss “why the benefits exceed the risks under the conditions stated in the labeling”); FDA, CRITICAL PATH OPPORTUNITIES REPORT R-8 (Mar. 2006) (discussing approval once “uncertainty” about benefit-risk balance has been “reduced to an acceptable level”); see also *United States v. Rutherford*, 442 U.S. 544, 555 (1979) (FDA “generally considers a drug safe when the expected therapeutic gain justifies the risk entailed by its use”).

¹⁴ FDA, PRESCRIPTION DRUG USER FEE ACT (PDUFA): ADDING RESOURCES AND IMPROVING PERFORMANCE IN FDA REVIEW OF NEW DRUG APPLICATIONS 17 (2005), <https://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFec/UCM149130.pdf> (“Knowledge about a product will always be limited to some extent at the time of approval by factors in the product development process.”).

¹⁵ A company with an approved new drug or biological product spends an average of \$312 million (capitalized to the point of market approval) on post-approval research and development. DiMasi, *supra* note 11, at 26–27.

¹⁶ E.g., Joshua Cohen & Kenneth Kaitin, *Follow-On Drugs and Indications: The Importance of Incremental Innovation to Medical Practice*, 15 AM. J. THERAPEUTICS 89, 90 (2008) (noting that the first-ever inhaled insulin was shown in clinical trials “to have a more rapid onset of action than other forms of injected insulin”).

¹⁷ E.g., Jörg Breitreutz & Joachim Boos, *Paediatric and Geriatric Drug Delivery*, 4 EXPERT OPINION ON DRUG DELIVERY 37, 37 (2006) (noting that children and the elderly struggle with swallowing solid oral dosage forms and fare better with liquid dosage forms, provided they are palatable); Albert I. Wertheimer & Thomas M. Santella, *Pharmacoevolution: The Advantages of Incremental Innovation* 9 (2005) (working paper), <http://www.who.int/intellectualproperty/submissions/en/Pharmacoevolution.pdf> (noting that new dosage forms for beta blockers allowed patients to customize their dosage regimens and provided liquids and chewable dosage forms for senior patients).

health outcomes.¹⁸ New combinations can simplify dosing regimens and increase patient compliance.¹⁹ New combinations can also provide safer options for patients than monotherapy; the classic example is fixed-dose combination regimens for treatment of HIV.²⁰

Innovators also routinely study their approved products in additional diseases and conditions. Some new uses may fall within the same therapeutic class, as when a cancer medicine is developed to treat additional cancers. For example, FDA approved Temodar (temozolomide) in 1999 for treatment of adult patients with refractory anaplastic astrocytoma (one type of brain tumor), and the drug is now also approved to treat newly diagnosed glioblastoma multiforme (another type of brain tumor).²¹ An example outside the cancer area would be Activase (alteplase), a blood clot dissolving agent approved in 1987 for treatment of acute myocardial infarction.²² FDA licensed this biologic in 1990 for treatment of acute massive pulmonary embolisms²³ and in 1996 for treatment of acute ischemic stroke.²⁴ In other instances, subsequent research may establish a product's potential in new therapeutic

¹⁸ E.g., J.-M.R. Detry et al., *Patient Compliance and Therapeutic Coverage: Comparison of Amlodipine and Slow Release Nifedipine in the Treatment of Hypertension*, 47 EUR. J. CLINICAL PHARMACOLOGY 477, 480 (1995) (finding that compliance and therapeutic coverage were superior with once-daily treatment to twice-daily treatment); L.A. Donnelly et al., *Adherence in Patients Transferred from Immediate Release Metformin to a Sustained Release Formulation: A Population-Based Study*, 11 DIABETES, OBESITY & METABOLISM 338, 340–41 (2009) (finding extended release metformin associated with increased adherence and improved glycemic control); Li Wang et al., *Effects and Patient Compliance of Sustained-Release Versus Immediate-Release Glipizides in Patients with Type 2 Diabetes Mellitus: A Systematic Review and Meta-Analysis*, 4 J. EVIDENCE-BASED MED. 232 (2011) (reviewing studies finding that “sustained-release glipizide appears to achieve similar glucose control with decreased insulin secretion, fewer hypoglycemic episodes, and higher patient compliance than immediate-release glipizide”). See also Wertheimer & Santella, *supra* note 17, at 11 (explaining that the development of controlled-release formulations for cardiovascular drugs led to once-daily nifedipine and once-weekly transdermal clonidine, both of which led to improved compliance and in turn decreased overall costs).

¹⁹ E.g., Ying-Chang Tung et al., *Medication Compliance and Clinical Outcomes of Fixed-Dose Combinations vs Free Combinations of an Angiotensin II Receptor Blocker and a Calcium Channel Blocker in Hypertension Treatment*, 19 J. CLINICAL HYPERTENSION 983, 987 (2017) (finding, in a retrospective analysis of 1136 patients in a claims database, that use of a fixed-dose combination “was associated with better medication adherence and persistence and survival free from [major adverse cardiac events] and hospitalization for heart failure”).

²⁰ Cohen & Kaitin, *supra* note 16, at 90 (“Another illustration is the HIV/AIDS combination product lopinavir/ritonavir, which was added to the [World Health Organization’s Essential Drug List] because of an improved safety and tolerability profile compared with the first-in-class drug, ritonavir.”).

²¹ Compare TEMODAR PACKAGE INSERT (1999), ¶¶ 141–48 with TEMODAR PACKAGE INSERT (Revised Oct. 2017), at 1.

²² Press Release, Genentech, Licensing of Activase Marks New Era in Treating Heart Attacks (Nov. 13, 1987), <https://www.gene.com/media/press-releases/4271/1987-11-13/licensing-of-activase-marks-new-era-in-t>.

²³ *2d Activase Approval*, N.Y. TIMES, June 7, 1990, at D4.

²⁴ ACTIVASE PACKAGE INSERT (Revised Jan. 2017), at 1; Carl T. Hall, *Activase Gets FDA Approval / Genentech Can Market Heart Drug for Strokes*, SF GATE (June 19, 1996, 4:00 AM), <https://www.sfgate.com/business/article/Activase-Gets-FDA-Approval-Genentech-can-market-2978288.php>.

categories. For example, FDA licensed Cimzia (certolizumab pegol) in 2008 for reducing the signs and symptoms of Crohn's disease, an inflammatory bowel disease that can lead to abdominal pain, severe diarrhea, fatigue, weight loss, and malnutrition.²⁵ This biologic is now also licensed for treatment of rheumatoid arthritis, active psoriatic arthritis, and active ankylosing spondylitis.²⁶ To give another example, FDA licensed Xgeva (denosumab) in 2010 for treatment of postmenopausal women with osteoporosis at high risk of fracture, and in 2013 it licensed this biologic for treatment of adults and skeletally mature adolescents with giant cell tumor of the bone that is unresectable.²⁷

Some research suggests that new-use innovation is especially common for biological products, which can treat a half dozen or more distinct conditions.²⁸ Avastin (bevacizumab) illustrates this. FDA approved Avastin in 2004 for the first-line treatment of patients with metastatic carcinoma of the colon and rectum.²⁹ Today, the product has six indications—one in colorectal cancer, plus indications relating to non-squamous non-small cell lung cancer, glioblastoma, metastatic renal cell carcinoma, cervical cancer, and recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer.³⁰

The inspiration for new-use research varies. Even during its premarket research program, a medicine's chemical class or mechanism of action may give rise to suspicions that it will treat more than one disease. The innovator may nevertheless defer investigation of additional indications while it generates the data necessary for initial marketing approval. Research and development of new medicines are expensive and time-consuming, and revenue from the initial approval can fund further research and development.³¹ In some cases, instead of deferring additional indications until after FDA approval, an innovator might take its planned indications into phase 3 one at a time. In other words, it might start the second indication in phase 2 (to settle on

²⁵ CIMZIA PACKAGE INSERT (Apr. 18, 2008), at 1.

²⁶ CIMZIA PACKAGE INSERT (Revised Jan. 2017), at 1. *See also* David E. Potter, *Can We Find New Uses for Old Drugs? One Word: Viagra*, STAT (Apr. 26, 2016), <https://www.statnews.com/2016/04/26/ketamine-drugs-repurposing/> (“There are a number of other promising candidates for repurposing: mecamylamine, ropinirole, and valsartan were all originally used for high blood pressure but are now being examined for treating depression, Parkinson’s disease, and Alzheimer’s disease, respectively. Tamoxifen, originally used for breast cancer, and amphotericin B, an antifungal drug, might both be useful in bipolar disorder.”).

²⁷ FDA, Xgeva BLA 125320 Approval Letter (June 1, 2010); FDA, Xgeva Supplement BLA125320/94 Approval Letter (June 13, 2013).

²⁸ *E.g.*, Maya Said et al., *CONTINUED DEVELOPMENT OF APPROVED BIOLOGICAL DRUGS: A QUANTITATIVE STUDY OF ADDITIONAL INDICATIONS APPROVED POSTLAUNCH IN THE UNITED STATES 3* (2007) (noting that 47% of biologics for recombinant DNA products and monoclonal antibodies regulated by CDER had at least one additional indication).

²⁹ AVASTIN PACKAGE INSERT (2004), ¶¶ 156–58 (2004).

³⁰ AVASTIN PACKAGE INSERT § 1 (2018).

³¹ DiMasi 2016, *supra* note 11, at 31 (estimating a total capitalized preapproval cost of developing a new drug or new biological product at 2.558 billion U.S. 2013 dollars).

dosage, among other things) once the first indication has gone into phase 3. Taking this staged approach can eliminate some of the financial risk to a company if the first indication fails, because the second indication will follow closely behind. To give an example, Ampyra (dalfampridine) completed its phase 2 trials for multiple sclerosis just a few months after the second phase 3 trial for treatment of spinal cord injury failed.³² If both indications succeed, the first indication leads to initial approval of the medicine, and work on the second indication leads to new-use approval within a few years.

Serendipity sometimes plays a role in inspiring new-use research. The initial premarket testing may have signaled an unexpected but promising additional use, which was deferred until after the initial application was submitted or even approved. A classic example is Evista (raloxifene). The trials supporting its approval in 1997 for osteoporosis prevention produced secondary data suggesting that breast cancer risk reduction was another possible use.³³ This eventually led to approval for two breast cancer indications.³⁴ In other cases, healthcare providers treating patients for one condition may have reported therapeutic benefits for seemingly unrelated conditions.³⁵ For example, the usefulness of thalidomide—which had been marketed as a sedative and antiemetic, though not in the United States—for treating the cutaneous symptoms of leprosy was discovered after a physician administered some, for sedation purposes, to a patient with mania and leprosy.³⁶

However they are discovered, later-developed uses can play a significant public health role. The classic example is interferon. FDA approved Intron A (interferon alfa-2b) in 1986 for treatment of hairy cell leukemia, a form of blood cancer that afflicts 1000 to 3000 Americans every year.³⁷ In 1991, the agency approved interferon for treatment of hepatitis C, a devastating bloodborne virus that causes severe liver damage over time, is the leading cause of cirrhosis and liver cancer, and affects more than 3 million people in the United States.³⁸ The drug company innovated further, combining interferon with ribavirin in 1998, and the cure rate rose to 42% for one genotype

³² Erika Lietzan, *The Drug Innovation Paradox*, 83 MO. L. REV. 39, 90–91 (2018).

³³ Henry G. Grabowski & Jeffrey L. Moe, *Impact of Economic, Regulatory, and Patent Policies on Innovation in Cancer Chemoprevention*, 1 CANCER PREVENTION RES. 84, 85 (2008).

³⁴ FDA, NDA 22-042, NDA 20-815/S-025 Approval Letter (Sept. 13, 2007).

³⁵ H. Subcomm. on Health & Env't, Comm. on Energy & Commerce, 97th Cong., Preliminary Report of the Survey on Drugs for Rare Disease 9 (Comm. Print 1982) (noting that sometimes drugs approved for common ailments are later discovered in the clinic—meaning by practicing physicians—to have the potential to treat a new disease).

³⁶ Sam F. Halabi, *The Drug Repurposing Ecosystem: Intellectual Property Incentives, Market Exclusivity, and the Future of "New" Medicines*, 20 YALE J.L. & TECH. 1, 31–32 (2018).

³⁷ *FDA to Approve Interferon for Use Against Rare Cancer*, N.Y. TIMES, June 5, 1986, at A20.

³⁸ PHRMA, TWENTY-FIVE YEARS OF PROGRESS AGAINST HEPATITIS C: SETBACKS AND STEPPING STONES 5–6, 9 (2014) [hereinafter PHRMA, TWENTY-FIVE YEARS].

of the virus.³⁹ This was followed by further incremental innovation—pegylation of the interferon molecule—to provide a longer half-life and then approval of the pegylated version in combination with ribavirin in 2001, fifteen years after FDA first approved interferon.⁴⁰ At the end of this sequence of incremental innovations, which started with a new-use discovery, the overall cure rate for hepatitis C leapt to 53%, and for two genotypes it soared to 70 to 80%.⁴¹ The new use of interferon fundamentally changed the prognosis for patients diagnosed with hepatitis C, and for ten years—until the development of protease inhibitors and polymerase inhibitors—it was the standard of care.⁴²

The importance of subsequent uses may be illustrated by the fact that in some therapeutic classes most of the actual use derives from indications approved later in time.⁴³ But it is also illustrated by the reverse: medicines approved for common ailments are sometimes later found useful in treating “orphan” diseases. An orphan disease affects fewer than 200,000 persons in the United States (or affects more, but there is no reasonable expectation that the cost of developing the treatment and making it available could be recovered from sales in the United States).⁴⁴ These diseases are considered “orphans” because the low revenue expected would ordinarily lead research-intensive companies to look elsewhere.⁴⁵ Developing approved medicines for new orphan uses contributes to the public health simply by addressing the unmet medical needs of patients suffering from rare diseases. Dozens of medicines have been developed for rare diseases after initial FDA approval for a more common ailment. To give an example, in 1993, FDA approved Lupron Depot-Ped (leuprolide acetate) to treat children with central precocious puberty, a rare disease in which puberty begins early, generally under the age of eight in girls and nine in boys.⁴⁶ The agency had originally approved

³⁹ Doris B. Strader, M.D. & Leonard B. Seeff, M.D., *A Brief History of the Treatment of Viral Hepatitis C*, 1 CLIN. LIVER DIS. 6, 6 (2012); FDA, NDA 20-903/S-001, S-002 Approval Letter (undated) (referencing approval of Rebetrone Combination Therapy Pak on June 3, 1998).

⁴⁰ Strader, *supra* note 39, at 6; *see also* Alan Franciscus, Hepatitis C Support Project, HCSP Fact Sheet: A Brief History of Hepatitis C 3 (2017).

⁴¹ Emilio Palumbo, *Pegylated Interferon and Ribavirin Treatment for Hepatitis C Virus Infection*, 2 THERAPEUTIC ADVANCES CHRONIC DISEASES 39, 42 (2011) (“Patients infected with HCV genotypes 2 or 3 have a 70–80% likelihood of [a sustained virological response] with a low dose of ribavirin and only 24 weeks of treatment.”); PEGASYS PACKAGE INSERT 5 (2003) (noting sustained virologic response to combination therapy in all patients at 53% and in genotypes 2–6 at 70%).

⁴² PHRMA, TWENTY-FIVE YEARS, *supra* note 38, at 11.

⁴³ Ernst R. Berndt et al., *The Impact of Incremental Innovation in Biopharmaceuticals*, 24 PHARMACOECONOMICS (SUPP. 2D) 69, 81 (2006) (finding that in some classes, 70–80% of total patient use was attributable to indications developed and approved after the drug first came to market).

⁴⁴ 21 U.S.C. § 360bb(a)(2) (Supp. IV 2012).

⁴⁵ As explained in Part II, we now have special incentives in place to address this market failure.

⁴⁶ *TAP’s Lupron Depot-Ped Available Week of April 26*, PINK SHEET (Apr. 26, 1993), <https://pink.pharmaintelligence.informa.com/PS022513/TAPs-LUPRON-DEPOTPED-AVAILABLE-WEEK-OF-APRIL-26>.

Lupron in 1985 for the palliative treatment of advanced prostate cancer, a far more common disease.⁴⁷

A new use for an approved drug may offer patients meaningful alternatives to treatments on the market. It might take the drug into a new therapeutic area, or fundamentally change the treatment paradigm for a common and serious disease, or offer long-sought relief for a previously untreated condition. No matter how and when it is discovered and developed, a new use of an approved drug can be profoundly important to patients and physicians.

II. INCENTIVES TO DEVELOP NEW USES

As Part I suggests, the full potential of a new medicine may not be apparent for years after its initial approval. But this continued research requires time and money. Although the investment required for a new use is generally less than the investment required to develop a new molecular entity from scratch, it is still substantial.⁴⁸ It can take three to six years and between \$100 and \$300 million to conduct the phase 2 and 3 trials needed to secure FDA approval of a new use.⁴⁹ In some cases, it can be much more expensive and take much longer. For instance, although the premarket trials of Evista signaled its potential use to treat breast cancer, and the first study in breast cancer (published two years after the drug's approval in osteoporosis) showed a

⁴⁷ PHYSICIANS' DESK REFERENCE 1804 (1986). The original product had been a short-acting subcutaneous injection, but the pediatric product for the new use was a long-acting intramuscular injection that could be administered monthly. Compare *id.* with TAP's Lupron Depot-Ped Available Week of April 26, *supra* note 46.

⁴⁸ The marketing application holder proposes the new use in a supplement to its original application, containing the results of new phase 3 studies and usually also new phase 2 studies. It is usually not necessary to reproduce laboratory, animal, or phase 1 human testing. For example, Abbott's 2007 supplement to its approved BLA for Humira (adalimumab), proposing treatment of adult patients with moderate to severe chronic plaque psoriasis, contained data from a phase 2 trial, two phase 3 trials, and four open-label trials. FDA, CENTER FOR DRUG EVALUATION AND RESEARCH, CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW sBLA 125057/110 at 2 (2007), https://www.accessdata.fda.gov/drugsatfda_docs/nda/2008/1250572110_ClinPharmR.pdf; FDA, CENTER FOR DRUG EVALUATION AND RESEARCH, MEDICAL REVIEW sBLA 125057/110 at 5 (2007), https://www.accessdata.fda.gov/drugsatfda_docs/nda/2008/125057s110_MedR_P1.pdf; FDA, CENTER FOR DRUG EVALUATION AND RESEARCH, PHARMACOLOGY REVIEW sBLA 125057/110 (2007), https://www.accessdata.fda.gov/drugsatfda_docs/nda/2008/125057s110_PharmR.pdf.

⁴⁹ Grabowski & Moe, *supra* note 33 (offering the \$100 million figure); Roin, *Solving the Problem*, *supra* note 7, at 24 n. 169 (offering the \$300 million figure) (citing Alison Sahoo, INDICATION EXPANSION: OPPORTUNITIES FOR SUCCESSFUL LIFECYCLE MANAGEMENT 28 (2007)); see also Said et al., *supra* note 28, at 6 ("[Post-approval development costs] are likely high and represent an important part of the overall R&D investment involved in researching and developing new therapeutic biologics."). In 2011, four innovators told the Supreme Court in an amicus brief that the cost of developing a new use was 40% less than the cost of developing a new molecular entity. Brief for Allergan, Inc. et al. as Amici Curiae supporting Respondents at *1, *Caraco Pharm. Labs. v. Novo Nordisk A/S*, 566 U.S. 399 (2012) (No. 10-844), 2011 WL 5073031.

secondary end point reduction in breast cancers, FDA required additional studies.⁵⁰ The agency did not approve Evista for its two breast cancer indications until 2007, after the company had conducted three additional controlled clinical trials in almost 30,000 women over nearly ten years.⁵¹

Patent protection and regulatory exclusivity provide the primary incentives to perform this research.⁵² The essence of both is the promise of a period of time to exploit the innovation without market competition.

First, federal patent law protects new uses of known compositions of matter. The Patent Act authorizes issuance of a patent for any “new and useful process, machine, manufacture, or composition of matter,” subject to the other requirements of the Act.⁵³ The inventor of a new and nonobvious composition may obtain a patent once he or she has identified both the

⁵⁰ Grabowski & Moe, *supra* note 33, at 85.

⁵¹ FDA, ELI LILLY & CO., LABELING-PACKAGE INSERT NDA 020815 § 14 (2018); FDA, Center for Drug Evaluation and Research, Medical Review NDA 22042, CLINICAL TEAM LEADER REVIEW OF SNDA, at 8 (2007), https://www.accessdata.fda.gov/drugsatfda_docs/nda/2007/022042s000_MedR_P1.pdf.

⁵² Some believe that the requirement and benefits of new drug approval provide an incentive to develop new drugs. Professor Katz has argued, for instance, that FDA’s imprimatur adds value to a drug, enabling a higher market price. Ariel Katz, *Pharmaceutical Lemons: Innovation and Regulation in the Drug Industry*, 14 MICH. TELECOMM. & TECH. L. REV. 1, 7 (2007); *see also* Eisenberg, *supra* note 7, at 725 (“FDA regulation fortifies the incentives of firms to invest in generating . . . socially valuable information . . . by requiring the submission of information as a precondition to bringing new products to market and to making marketing claims about products.”). They might also argue that the requirements and benefits of new-use approval provide a similar incentive. For instance, under current FDA rules, approval is necessary before a company may promote its drug for a new use, and the agency historically argued that the prohibition on “off-label promotion” ensures companies will conduct the trials necessary for new-use approval. *E.g.*, Wash. Legal Found. v. Friedman, 13 F. Supp. 2d 51, 70 (D.D.C. 1998) *amended by* 36 F. Supp. 2d 16 (D.D.C. 1999), *and amended by* 36 F. Supp. 2d 418 (D.D.C. 1999), *appeal dismissed sub nom.* Wash. Legal Found v. Henney, 56 F. Supp. 2d 81 (D.D.C. 1999), *and vacated in part*, 202 F.3d 331 (D.C. Cir. 2000) (“[T]he dissemination of information demonstrating that a drug is effective has a positive effect upon sales of the drug. But, if the manufacturer’s ability to disseminate any information on a new use for a previously approved drug is made wholly contingent upon FDA approval of that use, the manufacturer will be encouraged, if not compelled, to obtain FDA approval.”). Formal approval may also be necessary for insurance coverage. *See* Joshua Cohen et al., *Off-Label Use Reimbursement*, 64 FOOD & DRUG L.J. 391, 396–97 (2009) (reporting that in a study of 179 payers, one quarter exclude off-label use reimbursement altogether, and half of the remaining payers impose restrictions on this reimbursement). The response is that the requirement to seek approval is simply a legal barrier to labeling the drug for the new use in question. The barrier may *require* the work, but it does nothing to encourage a firm to invest resources in barrier-overcoming work in the first instance rather than in another venture altogether. The product’s subsequent position in the market must be sufficiently exclusive for the investment to have been profitable. Professor Eisenberg makes a similar point when she argues that the premarket approval paradigm for a new drug imposes a high barrier to entry for the company’s competitors, which provides a reward for innovation. Rebecca S. Eisenberg, *The Shifting Functional Balance of Patents and Drug Regulation*, 19 HEALTH AFFAIRS 119, 121 (2001), <https://www.healthaffairs.org/doi/pdf/10.1377/hlthaff.20.5.119>.

⁵³ 35 U.S.C. § 101 (2012).

composition and a utility for it.⁵⁴ The resulting patent generally entitles the inventor to exclude others from using the composition for all purposes.⁵⁵ In 1952, Congress amended the statute to state clearly that the term “process” includes “a new use of a known . . . machine, manufacture, composition of matter, or material.”⁵⁶ Thus, the original chemical composition and a later-discovered nonobvious new use for that composition are distinct patentable inventions. Put another way, if the inventor subsequently discovers a new and nonobvious use for the originally patented composition, he or she may obtain a separate patent for that use.⁵⁷ That second patent narrowly excludes

⁵⁴ *Id.*; *Brenner v. Manson*, 383 U.S. 519, 531 (1966) (reinstating decision of patent office that utility requirement had not been met when novel process yielded intended product but the applicant had failed to identify any specific and substantial utility for the resulting product); *Nelson v. Bowler*, 626 F.2d 853, 856 (CCPA 1980) (“Practical utility is a shorthand way of attributing ‘real-world’ value to claimed subject matter.”).

⁵⁵ 35 U.S.C. § 271(a) (2012) (any “use” of a patented composition is an infringing act).

⁵⁶ 35 U.S.C. § 100(b) (2012).

⁵⁷ *Id.* A trilogy of recent Supreme Court cases interpreting section 101 of the Patent Act—which governs eligibility for patents—may cast a shadow of uncertainty on new-use patents. *See generally* *Alice Corp. Pty. Ltd. v. CLS Bank Int’l*, 134 S. Ct. 2347 (2014); *Ass’n for Molecular Pathology v. Myriad Genetics, Inc.*, 569 U.S. 576 (2013); *Mayo Collaborative Servs. v. Prometheus Labs.*, 566 U.S. 66 (2012). No court has invalidated a patent claiming a new indication for an approved drug, such as treatment of breast cancer with a drug previously approved for osteoporosis. But courts have invalidated patents claiming new methods of using approved drugs. For instance, in September 2017, a lower court in Delaware applied the *Alice* framework to invalidate five patents that claimed methods of using INOmax (nitric oxide). *See generally* *Mallinckrodt Hospital Prods. IP Ltd. v. Praxair Distribution, Inc.*, No. 15-170-GMS, 2017 WL 3867649 (D. Del. Sept. 5, 2017), *aff’d in part & rev’d in part*, 890 F.3d 1024, 1038 (Fed. Cir. 2018) (ruling solely on the ‘112 patent). FDA approved INOMax for the treatment of term and near-term neonates with hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension. *See* *Praxair Distribution, Inc. v. Mallinckrodt Hospital Prods. IP Ltd.*, 890 F.3d 1024, 1028 (Fed. Cir. 2018). The claims at issue were directed to a method of treating patients with the product in a way that “reduces the risk that inhalation of nitric oxide gas will induce an increase in pulmonary capillary wedge pressure . . . leading to pulmonary edema.” ‘741 patent col. 14, ll. 28-33. The patent owner argued that this claim recites a new way to use an existing drug, specifically to reduce a particular adverse event. *Mallinckrodt Hospital Prods.*, No. 15-170-GMS, 2017 WL 3867649, slip op. at 16. The court nevertheless found the claims patent-ineligible, concluding that the effects of the compound were a matter of human physiology.” *Id.* at 20. Indeed, “[a]ny reaction to treatment with [the compound] will be a natural phenomenon, dictated by the patient’s physiological response to the drug.” *Id.* The claims recite “routine, conventional activity that does nothing to transform the law of nature” into patentable subject matter. *Id.* Although the court wrote that the claims were not “directed to a new way to use an existing drug,” *id.*, this ruling and others applying the Supreme Court’s recent 101 jurisprudence to new drugs may create some uncertainty for innovators about the robustness of the new-use patent incentive. *See, e.g.*, *Boehringer Ingelheim Pharms. v. HEC Pharm. Co.*, No. 15-cv-5982 (PGS)(TJB) 2016 WL 7177704, at *2 (D.N.J. Dec. 8, 2016) (granting motion to dismiss patent infringement claims because the claims—relating to the use of certain compounds for treating and/or preventing metabolic diseases—were directed to patent ineligible subject matter); *Order Granting Defendant’s Motion for Judgment on the Pleadings, Nat. Alts. Int’l, Inc. v. Creative Compounds, LLC*, No. 16-cv-02146-H-AGS, 2017 WL 3877808, at *7 (S.D. Cal. Sept. 5, 2017) (invalidating on patent eligibility grounds a patent claiming a method of using beta-alanine in dietary supplement form to increase anaerobic working capacity in human subjects and one claiming a method of manufacturing a dietary supplement to increase beta-alanyl

others from only the newly discovered use, not any other use of the composition.⁵⁸

Second, for more than thirty years, the Federal Food, Drug, and Cosmetic Act ("FDCA") has provided three years of regulatory exclusivity for a new use of a previously approved drug, if approval of the use required clinical data other than bioavailability data.⁵⁹ This is separate from the five-year "new chemical entity" ("NCE") exclusivity that may attach when a drug is first approved.⁶⁰ The five-year NCE exclusivity is somewhat analogous to the original composition of matter patent. And like a new-use patent, new-use exclusivity protects subsequent innovation. New-use exclusivity prohibits FDA from approving a generic drug for the new use in question.

The three-year exclusivity provision was added to the pending generic drug legislation in August 1984 after a group of the country's largest research-based companies expressed concerns about language then under consideration.⁶¹ That language would have provided four years of exclusivity for new active ingredients first approved after enactment and ten years for new active ingredients first approved in the two years before enactment.⁶² The research-based companies responded in part by explaining the importance of incremental innovation. They explained that these innovations "frequently are as important and contribute as much to the public health as the active ingredients covered under the provision."⁶³ A compromise brokered by Senator Orrin Hatch and Representative Henry Waxman in early August resulted in the addition of exclusivity for all new conditions of use, including new indications, supported by clinical data.⁶⁴

histidine levels in muscle tissues sufficiently to delay onset of fatigue in humans). The author is grateful to Professor Karshedt for bringing the beta-alanine case to her attention.

⁵⁸ Another party could discover and patent the new and nonobvious use, but it would not be able to use the new discovery without infringing the original inventor's composition patent.

⁵⁹ 21 U.S.C. § 355(j)(5)(F)(iv). Bioavailability refers to "the rate and extent to which an active ingredient or [active moiety] is absorbed from a drug and becomes available at the site of drug action." 21 C.F.R. § 314.3(b).

⁶⁰ Biologics receive twelve years of regulatory exclusivity when they are first licensed. 42 U.S.C. § 262(k)(7). Unlike non-biological drugs, they are not eligible for new-use regulatory exclusivity.

⁶¹ See Drug Price Competition and Patent Term Restoration Act of 1984: Hearing on S. 2748 Before the S. Comm. on Labor & Human Res., 98th Cong. 108 (1984). Prior to September 1984, federal law did not provide a statutory pathway for approval of abbreviated applications for generic drugs. Cf. H.R. REP. NO. 98-857, pt. 1, at 1 (1984) (creating a stator pathway for approval of abbreviated applications for generic drugs).

⁶² H.R. REP. NO. 98-857, pt. 1, at 15-16 (1984) (creating a four-year exclusivity period for unpatentable drugs only).

⁶³ Drug Price Competition and Patent Term Restoration Act of 1984: Hearing on H.R. 3605 Before the S. Comm. on Labor & Human Res., 98th Cong. 108 (1984) (statement on behalf of ten companies). Over the summer, these companies focused mainly on ensuring that new-use approvals in the two-year transition window from 1982 to 1984 would receive exclusivity. See *id.*

⁶⁴ Alan D. Lourie, *Patent Term Restoration*, 66 J. PAT. OFF. SOC'Y. 526, 547-48 (1984).

On the Senate floor, Senator Hatch described the new exclusivity language, explaining that new drug applications for new chemical entities would receive five years of exclusivity going forward, and other applications supported by clinical data would receive three years.⁶⁵ He offered an amendment (which was accepted): additional language that would provide exclusivity for incremental innovation proposed in supplemental applications after initial approval.⁶⁶ This would protect “alterations” to approved drugs—like new indications, he said—“which require considerable time and expense in FDA required clinical testing.”⁶⁷ In September, when the House considered the language, Representative Waxman explained that this “period of exclusive market life” was intended to “encourage drugmakers to obtain FDA approval for significant therapeutic uses of previously approved drugs.”⁶⁸ If a company invested money in a new use that was “significant enough to require clinical tests,” the drafters had adopted the “principle” that “we are going to protect their investment for 3 years,” which Representative Waxman viewed as “reasonable.”⁶⁹

Third, since 1983 the FDCA has also offered seven years of regulatory exclusivity for new drugs and biological products developed to treat rare diseases and conditions.⁷⁰ Like three-year exclusivity, orphan exclusivity is use exclusivity. It protects the use, rather than the underlying compound, because it prohibits FDA approval of another application for the same compound for the same use.⁷¹ Orphan exclusivity is powerful, because it blocks not only abbreviated applications (for generic drugs and biosimilars) but also full applications from other innovators who propose the same use. For biologics innovators who do not have the option of three-year exclusivity for new uses, orphan exclusivity is the only regulatory exclusivity available for a new indication.

Orphan exclusivity is available not only for a medicine’s initial use, but also for a new use proposed in a supplemental application. And it is available even if the first approved use was not an orphan indication. Indeed, dozens

⁶⁵ 130 Cong. Rec. 23,765 (1984) (statement of Sen. Hatch).

⁶⁶ *Id.* at 23,765–66 (adding language that now appears in section 505(j)(5)(F)(iv) of the FDCA).

⁶⁷ *Id.* at 23,766.

⁶⁸ *Id.* at 24,425.

⁶⁹ *Id.* at 24,436 (statement of Rep. Waxman).

⁷⁰ 21 U.S.C. § 360cc(a) (2012). As initially enacted, the scheme protected only unpatentable products. Orphan Drug Act, Pub. L. No. 97-414, § 2, 96 Stat. 2049, 2050–51 (1983). Congress extended the incentive to all drugs and biologics in 1985. Orphan Drug Amendments of 1985, Pub. L. No. 99-91, § 2, 99 Stat. 387, 387 (1985).

⁷¹ 21 U.S.C. § 360cc(a)(2) (stating that FDA “may not approve another application . . . or issue another license” for the same drug for the same disease or condition). *See also* H.R. REP. NO. 97-840, pt. 1, at 9 (1982) (“A drug can be tested and approved for more than one use. Many of the currently marketed drugs for rare diseases are also used in common diseases. The designation process established by the bill avoids this confusion by *designating the use of the drug* which is for a rare disease or condition.” (emphasis added)).

of drugs first approved for more common ailments have received orphan exclusivity for later developed uses, including Abraxane (paclitaxel) (first for breast cancer and eight years later for pancreatic cancer), Halaven (eribulin mesylate) (first for metastatic breast cancer and six years later for liposarcoma), and Votrient (pazopanib) (first for renal cell carcinoma and three years later for advanced soft tissue sarcoma).⁷² Offering orphan exclusivity for new uses of drugs already marketed for common diseases was a deliberate choice. In a report prepared to inform consideration of the pending orphan drug legislation, Representative Waxman's subcommittee noted that a meaningful number of drugs are developed first for a common condition and only later for an orphan indication.⁷³

Patent protection for new uses, three-year regulatory exclusivity for new uses, and seven-year regulatory exclusivity for new orphan uses have the same goal and are similar in how they are intended to operate. All are meant as incentives for new-use innovation. Each provides an incentive by promising a period of time during which a company's competitors will not benefit from sales of their own versions of the medicine for the use in question. Each erects a temporary legal barrier to competition so the new use is excludable for a time. None are intended to prevent the company's competitors from marketing the underlying compound for another use (provided any relevant patents and exclusivity have expired or a license has been paid). And, as written, none should have this broader effect; each is tailored to protect only the new use in question.

III. THE VOIDING OF NEW-USE PATENTS AND EXCLUSIVITY

Patent protection, three-year exclusivity, and orphan exclusivity are meant to operate as temporary barriers to market entry, but in practice they do not work this way. Drug innovators lose new-use sales to their generic competitors. This stems from a pernicious combination of FDA policies and practices, state laws, and prescriber, generic industry, and payer practices, none of which are necessary for patients and payers to benefit from generic copies of no-longer-protected drugs and uses. Moreover, under current law it is nearly impossible for drug innovators to prevent these sales or obtain relief after the fact.

⁷² FDA, Abraxane NDA 21-660 Approval Letter (2005); FDA, Abraxane NDA 21660/S-037 Supplement Approval Letter (2013); FDA, Halaven NDA 201532 Approval Letter (2010); FDA, Halaven NDA 201532/S-015 Supplement Approval Letter (2016); FDA, Votrient NDA 022465 Approval Letter (2009); FDA, Votrient NDA 022465/S-010/S-012/PMR 1549-5 Supplement Approval Letter (2012).

⁷³ See H.R. Subcommittee on Health and the Environment of the Committee on Energy and Commerce, 97th Cong., Preliminary Report: Survey on Drugs for Rare Disease 7 (1982) (Comm. Print 97-BB).

Biologics innovators may similarly lose new-use sales to their biosimilar competitors, but the framework for biosimilars is new, and we know very little still about innovation and competition in the biosimilar marketplace.⁷⁴ The incentives for new-use innovation are different, however, as already noted. For instance, although biologics innovators are eligible for seven-year new-use orphan exclusivity, they are not eligible for three-year regulatory exclusivity for ordinary new uses. The rules governing approval of biosimilar biologics are different, and the markets are likely to function very differently.⁷⁵ Some of the factors that contribute to the voiding of new-use patents and new-use regulatory exclusivity for drugs are likely to apply equally to new-use patents and regulatory exclusivity for biologics, but exploring the likely differences is beyond the scope of this Article. And it may be premature, because FDA has approved only a handful of biosimilar biologics (and no interchangeable biologics). The discussion below focuses primarily on new uses for drugs.

A. *Practices and Policies that Undermine Patents and Regulatory Exclusivity*

FDA decided decades ago that the regulatory provisions of the FDCA authorize approval of a generic drug with labeling that omits indications protected by exclusivity or patent.⁷⁶ The omission is called a “carve-out,” and the resulting generic labeling is called partial labeling, or sometimes “skinny labeling” or “carved-out labeling.” When Bristol-Myers Squibb (“BMS”) faced generic versions of Capoten (captopril) labeled only for hypertension, with two exclusivity-protected indications carved out, the company argued—not unreasonably—that FDA’s decision was not authorized by the statute.⁷⁷ The statute requires the labeling of a generic drug to be the “same” as the labeling of the corresponding innovative drug.⁷⁸ The statute makes two exceptions, neither of which appears to cover omissions due to patents or exclusivity.⁷⁹ Specifically, the same-labeling provision permits differences

⁷⁴ See Lietzan, *supra* note 4, at 926, 928, 937, 939.

⁷⁵ See *id.* at 894.

⁷⁶ See 21 C.F.R. § 314.94(a)(8)(iv) (2017) (“Labeling . . . proposed for the drug product must be the same as the labeling approved for the reference listed drug, except for . . . omission of an indication or other aspect of labeling . . . accorded exclusivity under § 505(j)(5)(F).”).

⁷⁷ See *Bristol-Myers Squibb Co. v. Shalala*, 91 F.3d 1493, 1499 (D.C. Cir. 1996).

⁷⁸ 21 U.S.C. § 355(j)(2)(A)(v) (2012) (generally requiring application to contain information to show that the labeling proposed for the new drug is the same as the labeling approved for the listed drug); *id.* § 355(j)(4)(D)(ii) (listing lack of same labeling as a ground for refusal to approve a generic application).

⁷⁹ *Id.* § 355(j)(2)(A)(v) (permitting “changes required because of differences approved under a [suitability petition] or because the [generic] drug and the [innovative] drug are produced or distributed by different manufacturers”).

needed because FDA allowed the generic company to change its route of administration, dosage form, strength, or one of multiple active ingredients. It also permits differences “required” because the drugs are produced or distributed by different companies.⁸⁰ The former authorizes only specific listed differences, which do not include differences in approved indications. The latter arguably does not authorize differences due to patent or exclusivity, because a difference in the companies does not “require” different labeling in that situation. After all, the generic company could seek a license from the patent or exclusivity holder to label its product with the protected use.

FDA nevertheless decided that the plain language of the statutory same-labeling provision permitted generic captopril applicants to omit indications for which BMS held exclusivity.⁸¹ The agency further relied on a 1984 report from the House Committee on Energy and Commerce, which stated that the proposed legislation “permits [a generic drug] to be approved for less than all of the indications for which the listed drug has been approved.”⁸² This passage relates to patented uses and appears in a summary of the generic drug bill as it stood in June 1984, before the bill was amended to provide regulatory exclusivity for new uses. The D.C. Circuit, reviewing FDA’s decision, was not persuaded that the timing mattered and concluded that FDA’s approach of permitting exclusivity carve-outs “finds unusually strong support in the legislative history.”⁸³ The court reasoned that Congress must have added the new-use exclusivity provision understanding that the generic approval provisions would not prevent approval of partial labeling. Thus, FDA could approve generic versions of Capoten for hypertension, despite the fact that BMS held exclusivity for diabetic nephropathy and left ventricular dysfunction following myocardial infarction. As a result, it has been clear since 1996 that neither new-use exclusivity nor new-use patent protection protects an innovator from a generic copy that is labeled only for unprotected indications. FDA also applies this policy to biosimilar biologics, even though they are not subject to a statutory “same labeling” requirement in the first instance.⁸⁴ For example, it allowed Amgen to omit three indications and a

⁸⁰ *Id.*

⁸¹ Brief for Appellees at 29, *Bristol-Myers Squibb Co. v. Shalala*, 91 F.3d 1493 (D.C. Cir. 1996) (No. 95-5399).

⁸² *Id.* at 29–30 (citing H.R. REP. NO. 98-857, pt. 1, at 21–22, reprinted in 1984 U.S.C.C.A.N. 2654–55). This discussion in the legislative history relates to a statutory provision that contemplates generic applicants choosing not to seek approval for some uses protected by *patent*. 21 U.S.C. § 355(j)(2)(A)(viii) (2012) (allowing a generic applicant to include, in its application, a statement that a method of use patent listed in the Orange Book does not claim a use for which the applicant is seeking approval). Neither the statute nor the legislative history explains how this provision is to be reconciled with a same-labeling requirement that contains no exception for avoidance of patents.

⁸³ *Bristol-Myers Squibb Co. v. Shalala*, 91 F.3d 1493, 1500 (D.C. Cir. 1996).

⁸⁴ Compare 21 U.S.C. § 355(j)(2)(A)(v) (requirement that a generic application show that the generic labeling is the same as the reference listed drug labeling) with 42 U.S.C. § 262(k)(2)(A)(i) (2012) (requirements for a biosimilar application, which do not include this requirement). See also U.S. FOOD &

patient population for a fourth indication from the labeling of Amjevita (adalimumab-atto), its biosimilar of Humira (adalimumab).⁸⁵

The fact that in a particular case a generic may be dispensed almost exclusively for the protected use does not change FDA's approach and has not swayed the courts. This became clear in a 2002 case involving levocarnitine.⁸⁶ The innovator first secured approval for metabolism errors and later obtained approval for end stage renal disease ("ESRD"). Its product was available in oral dosage forms and an injectable form, but only the injectable form was approved for treatment of ESRD. Moreover, over 80% of the sales of the injectable product were for ESRD. FDA approved two generic drugs while the innovator held orphan exclusivity for ESRD, even though the generic companies planned to market only the injectable form of the product. In other words, it was unavoidable (and probably intended) that the generic drugs would be used primarily for the use that was protected and that had been omitted from their labeling. The Fourth Circuit affirmed, clearing the path for generic companies to sell products that everyone understood would mostly be used for an indication for which another company was entitled to exclusive sales. The court reasoned that the plain language of the statute permitted approval.⁸⁷

This outcome is troubling because FDA could have refused the approval. The agency's orphan drug regulations preclude approval of a second drug "intended for the same use" during the exclusivity term, and the agency's intended use regulation authorizes it to consider "the circumstances that the article is, with the knowledge of the [applicant], offered and used for a purpose for which it is neither labeled nor advertised."⁸⁸ No court had ever found a product's intended use without relying on the manufacturer's express claims, however, and FDA declined to do so here.⁸⁹ The agency has also rejected arguments that a generic drug in this situation—likely to be used for an indication carved out of its labeling—is "misbranded" under sections

DRUG ADMIN. GUIDANCE FOR INDUSTRY, BIOSIMILARS: QUESTIONS AND ANSWERS REGARDING IMPLEMENTATION OF THE BIOLOGICS PRICE COMPETITION AND INNOVATION ACT OF 2009 8 (2015) 8 ("[A] biosimilar applicant generally may obtain licensure for fewer than all conditions of use for which the reference product is licensed.").

⁸⁵ Amgen omitted pediatric Crohn's disease, hidradenitis suppurativa, uveitis, and juvenile idiopathic arthritis for patients between the ages of two and four. *Compare* HUMIRA PACKAGE INSERT § 1 (2016) with AMJEVITA PACKAGE INSERT § 1 (2016).

⁸⁶ *Sigma-Tau Pharm. Inc. v. Schwetz*, 288 F.3d 141, 147–148 (4th Cir. 2002).

⁸⁷ *Id.* at 144–45.

⁸⁸ 21 C.F.R. § 201.128 (2017). The orphan drug regulations explain that during the exclusivity term, FDA will not approve another company's marketing application "for the same drug" for the same use. 21 C.F.R. § 316.31 (2017). They also define "same drug" for purposes of orphan drug exclusivity for small molecule drugs to mean "a drug that contains the same active moiety as a previously approved drug and is intended for the same use as the previously approved drug." 21 C.F.R. § 316.3(b)(13)(i).

⁸⁹ The court deferred to FDA's interpretation and application of its regulations. *Sigma-Tau*, 288 F.3d at 146.

502(a) and 201(n) of the act because its labeling omits facts that are “material with respect to consequences which may result from . . . conditions of use as are customary or usual.”⁹⁰

As a result of the agency decisions and court cases just described, the agency’s partial labeling policy is settled law.⁹¹ Thus, as a general rule, subsequent innovation by an innovator does not block prompt approval of another company’s application once the compound patent and regulatory exclusivity have expired and the initial indication is no longer protected. In theory, the generic company may sell its product for the unprotected uses, and the innovator will still enjoy exclusive sales for the protected uses. That is, after all, the purpose of the innovator’s new-use patent and regulatory exclusivity. But exclusive sales turn out to be impossible.

Not only will FDA approve a generic drug that omits a protected indication from its labeling, but the agency will also deem that generic drug “therapeutically equivalent” to the innovator’s product. In the 1970s, the states began to adopt laws and regulations to encourage or require the substitution of less expensive drug products for brand products that had been prescribed.⁹² These states asked FDA for assistance in preparing formularies that would list the drugs that were, or were not, substitutable.⁹³ The agency responded in 1979 with a draft list of all prescription drugs approved as safe and effective, along with “therapeutic equivalence” decisions for any distributed by more than one company.⁹⁴ The basic idea was that two products deemed therapeutically equivalent could be substituted for each other, “with the full expectation that the substituted product will produce the same clinical

⁹⁰ 21 U.S.C. §§ 321(n), 352(a) (2012). This arose in connection with Marinol (dronabinol), a synthetic cannabinoid approved for treatment of nausea and vomiting associated with cancer chemotherapy and for treatment of appetite loss associated with weight loss in patients with AIDS. In 2007, generic applicants sought approval without the patent-protected AIDS indication. *See* Solvay Pet. at 2, Docket No. FDA-2007-P-0169 (Oct. 25, 2007). The NDA holder, Solvay, pointed out that two-thirds of the patients receiving Marinol were AIDS patients and that omitting the AIDS indication also necessarily entailed omitting information about daily dose, timing of administration, duration of treatment, and central nervous system adverse events for these patients. *Id.* at 3–6. This, Solvay argued, meant the labeling would omit facts that were material with respect to a customary or usual use. *Id.* at 2. The FDA was unwilling to consider the likely off-label use, because doing so would “nullify” the provisions of the statute that it had already interpreted to permit carve-outs. FDA Letter to Solvay Pharmaceuticals 10, Docket No. FDA-2007-P-0169 (Apr. 25, 2008).

⁹¹ There is one exception to the partial labeling policy, which rarely applies (i.e. if a generic drug would be less safe and effective than the innovative drug for its labeled uses, the carve-out is not permitted). 21 C.F.R. § 314.127(a)(7). In this case, FDA cannot approve the generic drug until the relevant patent and regulatory exclusivity expire or the generic company obtains a license. *See id.*

⁹² Henry G. Grabowski & John M. Vernon, *Substitution Laws and Innovation in the Pharmaceutical Industry*, 43 LAW & CONTEMP. PROBS. 43, 49 (1979).

⁹³ FDA, APPROVED DRUG PRODUCTS WITH THERAPEUTIC EQUIVALENCE EVALUATIONS, at iv (38th ed. 2018) [hereinafter 38TH ORANGE BOOK].

⁹⁴ *Id.*

effect and safety profile as the prescribed product.”⁹⁵ FDA finalized the list in October 1980, publishing it in a paperback known in the industry as the Orange Book.⁹⁶ Since then, the agency has issued monthly supplements and reissued the book in its entirety once a year. Today the Orange Book, now in its 38th edition, is also available as a searchable database on the agency’s website.⁹⁷

When making therapeutic equivalence determinations, FDA does not consider the scope of a drug’s approval. Instead, as the preface to the Orange Book explains, the agency deems two products therapeutic equivalents (designates them as “AB rated”) if they are pharmaceutical “equivalents for which bioequivalence has been demonstrated.”⁹⁸ Two products are “pharmaceutical equivalents if they [have] the same active ingredients, . . . route of administration,” dosage form, and strength.⁹⁹ Two products are bioequivalent if they are pharmaceutical equivalents (or alternatives¹⁰⁰) and display comparable bioavailability “under similar experimental conditions.”¹⁰¹ Put another way, FDA defines therapeutic equivalence as a function of tangible product features and bioavailability in the body, not the scope of regulatory approval.

The agency has structured the Orange Book to avoid limiting the scope of its advice to approved indications. The publication does not differentiate between generic drugs approved for all the innovative drug’s indications and generic drugs that lack some indications.¹⁰² Therapeutic equivalence ratings do not indicate that the therapeutic equivalence decision refers only to the approved indications or to certain specific indications. FDA recently abandoned a modest caveat about unapproved uses that it previously included in the Orange Book. From 1996 through 2016, the preface stated that

⁹⁵ *Id.* at vii–viii.

⁹⁶ *Id.* at v. After enactment of the generic drug legislation in 1984, the agency added information about each drug’s unexpired patents and regulatory exclusivity. See FDA, APPROVED DRUG PRODUCTS WITH THERAPEUTIC EQUIVALENCE EVALUATIONS (6th ed. 1985).

⁹⁷ See FDA, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations (last visited Sept. 30, 2018), <https://www.accessdata.fda.gov/scripts/cder/ob/index.cfm>.

⁹⁸ 38TH ORANGE BOOK, *supra* note 93, at vii. FDA uses a variety of “A” codes to designate therapeutic equivalence: AA, AN, AO, AP, and AT (“depending on the dosage form”) for drugs as to which “there are no known or suspected bioequivalence problems,” and AB for drugs as to which “actual or potential bioequivalence problems have been resolved with adequate *in vivo* and/or *in vitro* evidence.” *Id.* at xiii. This Article simply refers to “AB” rating, for therapeutic equivalence, which is the convention.

⁹⁹ *Id.* at vii.

¹⁰⁰ Pharmaceutical alternatives have “the same therapeutic moiety, but [either have] different salts, esters, or complexes of that moiety, or [have] different dosage forms or strengths.” *Id.*

¹⁰¹ *Id.* at viii. For instance, two drugs are bioequivalent if there is not “a significant difference in the rate and extent” of their absorption “when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions.” *Id.*

¹⁰² The Orange Book does not specify the indications for which a drug is approved. One would have to determine this from the labeling. The brand labeling is usually available on FDA’s website, but often the generic labeling is not.

therapeutic equivalence decisions “are not made for unapproved, off-label uses.”¹⁰³ In the 2017 edition, however, the agency deleted this proviso without comment. In short, for the more than thirty years that FDA has published the Orange Book, it has provided a flat AB rating once a generic drug is approved.

FDA did not need to take this “generic for one use, generic for all uses” approach. The agency invented the concept of therapeutic equivalence before Congress enacted the Hatch-Waxman Amendments permitting approval of generic drugs. The statute says nothing about providing therapeutic equivalence ratings, and the agency could stop providing these ratings—or change the system entirely—without legislative action. Moreover, the current language in the Orange Book provides a basis for considering the scope of generic approval when issuing AB ratings. For instance, it states that two products must be “adequately labeled” to be therapeutically equivalent.¹⁰⁴ It also states that therapeutic equivalents “can be expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling.”¹⁰⁵ Both passages provide a basis for indication-specific ratings. But FDA has never taken the position that the two must be labeled for the same uses to be deemed therapeutically equivalent. Instead, it provides an AB rating to a bioequivalent and pharmaceutically equivalent generic drug that omits protected uses from its labeling. The preface explains that such a generic “can be substituted with the full expectation that [it] will produce the same clinical effect and safety profile as the prescribed product.”¹⁰⁶

FDA’s decision to provide a blanket AB rating means that as a general rule the generic drug will be dispensed whenever the innovator’s drug is prescribed, including for new uses under patent protection or regulatory exclusivity. This is because FDA’s therapeutic equivalence decisions facilitate, and in some cases trigger, substitution under state pharmacy law. Although the precise wording varies, in every state the law authorizes (and in some cases, it requires) a pharmacist to substitute a therapeutically equivalent generic drug when filling a prescription for a brand product.¹⁰⁷ State medical practice laws do not require a physician to specify the patient’s condition or the intended use of a medicine on the prescription form. State pharmacy acts and pharmacy board regulations generally do not require a pharmacist to inquire about the patient’s condition or the intended use of a prescribed drug

¹⁰³ *E.g.*, FDA, APPROVED DRUG PRODUCTS WITH THERAPEUTIC EQUIVALENCE EVALUATIONS, at vii (36th ed. 2016).

¹⁰⁴ 38TH ORANGE BOOK, *supra* note 93, at vii.

¹⁰⁵ *Id.*

¹⁰⁶ *Id.*

¹⁰⁷ *See* New York ex rel. Schneiderman v. Actavis PLC, 787 F.3d 638, 644–45 (2d Cir. 2015) (“Although the specific terms of these laws vary by state, drug substitution laws either permit or require pharmacists to dispense a therapeutically equivalent, lower-cost generic drug in place of a brand drug absent express direction from the prescribing physician that the prescription must be dispensed as written.”).

or to verify that a generic drug is approved for the use before substituting the generic drug for the innovative drug prescribed. Payers generally require substitution of a drug that is both bioequivalent and pharmaceutically equivalent without regard to the patient's condition or the scope of the dispensed drug's approval.¹⁰⁸

By shifting sales to the generic product even for a new use, state laws and payer policies allow generic drugs to flow past the temporary barrier to entry created by federal patent law and regulatory exclusivity law. FDA's blanket approach to AB ratings makes this possible, in part by eliminating any incentive for the generic company to seek a license from the innovator. If a generic company paid the innovator for a license to label its drug for the protected use, the generic drug would be approved for the use and listed as AB-rated. But if the generic company declined to pay for a license, its generic drug, despite lacking approval for the use, would also be listed as AB-rated. State law and payer policies would lead to substitution in either case. Absent a meaningful risk of liability for these sales, the generic company has no incentive to seek a license.¹⁰⁹

If automatic substitution does not lead to infringing sale and use, prescribing decisions may nevertheless still do so. That is, a healthcare provider might select a generic drug or a biosimilar biologic for an unapproved use for which the innovator holds approval and a new-use patent or regulatory exclusivity. FDA generally does not step in when healthcare professionals prescribe drugs for unapproved uses.¹¹⁰ Its practice of medicine policy states that once a new drug (which includes a generic drug) is in a local pharmacy after interstate shipment, "the physician may, as part of the practice of medicine, lawfully . . . vary the conditions of use from those approved in the

¹⁰⁸ See, e.g., BOSTON MEDICAL CENTER HEALTHNET PLAN, PHARMACY POLICY: MANDATORY GENERIC SUBSTITUTION PROGRAM (Mar. 2, 2018), <https://www.bmchp.org/~media/e5e4b16fbc414928abc005786257714f.pdf> (stating that once FDA has granted an A rating to the generic drug, the plan will cover the brand product *only* if the patient has an allergy to an inactive ingredient in the generic drug or the patient has not responded adequately to at least two other covered drugs in the same class). State health insurance laws do not require a different approach. See, e.g., N.J. REV. STAT. § 17B:27F-3 (2017) (requiring only that a pharmacy benefit manager determine that the drug is listed as therapeutically and pharmaceutically equivalent in the ORANGE BOOK).

¹⁰⁹ The same thing may happen once FDA starts to approve interchangeable biologics. Biosimilar biologics are not substitutable. Instead, "interchangeable biologics"—subject to a different approval standard—are substitutable. 42 U.S.C. § 262(k)(4) (2012) (stating the approval standard for interchangeable biologics); § 262(i)(3) (stating that interchangeable biologics "may be substituted for" the corresponding innovative product "without the intervention of" the prescriber). FDA has approved biosimilar biologics with patent-protected and orphan-exclusivity-protected uses omitted from their labeling, and although the question is not yet resolved it may decide to approve interchangeable biologics with partial labeling. In this case, pharmacists might substitute the interchangeable biologic for the prescribed innovative product, even though the innovator was meant to have exclusive sales for the use in question.

¹¹⁰ There is one exception. Section 333(e) of the FDCA makes it a felony to distribute human growth hormone (including by administering it directly to a patient) for a use that FDA has not approved. See 21 U.S.C. § 333(e) (2012).

package insert, without informing or obtaining the approval of the Food and Drug Administration.”¹¹¹ State laws also generally permit physicians to prescribe approved drugs for unapproved uses.¹¹²

FDA’s practice of medicine policy arose to accommodate use of innovative products beyond the scope of their labeling. It acknowledges that the standard of care may move more quickly than federal regulators.¹¹³ It also acknowledges that it may be appropriate for a healthcare professional to choose an investigational use of an approved medicine when in his or her clinical judgment—and with the patient’s consent—that use is in the patient’s best interest.¹¹⁴ On the whole, it is a sound policy. The problem comes from extending the policy to prescribing a generic drug or biosimilar for an unapproved use simply because the innovator’s product (which is approved for that use) is more expensive. While using the innovator’s product for the new use may raise affordability issues, the prospect of financial reward from market exclusivity provided the incentive to develop the new use in the first instance. If we are committed to the patent and exclusivity laws as they are currently written and intended to function, then off-label prescribing for infringing uses to save money—to avoid exclusivity—is a problem.

Yet prescribers receive encouragement and even instructions about infringing uses of generic drugs and biosimilars. The most significant source is what might be called a “noisy carve-out.” Thanks to recent amendments to the FDCA, if an innovator’s patent or regulatory exclusivity precludes approval of a generic drug for a new pediatric indication, the generic drug’s labeling may nevertheless signal its safety and effectiveness for the

¹¹¹ 37 Fed. Reg. 16,503 (Aug. 15, 1972). Regulating the practice of medicine generally falls to the states. Patricia J. Zettler, *Toward Coherent Federal Oversight of Medicine*, 52 SAN DIEGO L. REV. 427, 430–31 (2015) (“[T]he conventional wisdom among courts, lawmakers, and administrative agencies is that states regulate medical practice, while the federal government regulates medical products.” (emphasis omitted)).

¹¹² See Sandra H. Johnson, *Polluting Medical Judgment? False Assumptions in the Pursuit of False Claims Regarding Off-Label Prescribing*, 9 Minn. J.L. Sci. & Tech. 61, 68 (2008) (“State liability standards . . . generally do not place the physician at significantly increased risk of liability for off-label prescribing per se.”).

¹¹³ See, e.g., PETER BARTON HUTT ET AL., FOOD AND DRUG LAW 814 (4th ed. 2014). Indeed, off-label use may be recommended by applicable clinical guidelines. See Randall S. Stafford, *Regulating Off-Label Drug Use: Rethinking the Role of the FDA*, 358 NEW ENG. J. MED. 1427, 1427 (2008).

¹¹⁴ See FDA, MEMORANDUM: PUBLIC HEALTH INTERESTS AND FIRST AMENDMENT CONSIDERATIONS RELATED TO MANUFACTURER COMMUNICATIONS REGARDING UNAPPROVED USES OF APPROVED OR CLEARED MEDICAL PRODUCTS 17 (2017) (“Health care providers prescribe and use medical products for unapproved uses when they judge that the unapproved use is medically appropriate for their particular patients—whose characteristics and needs may differ from the characteristics of the population studied for the approved/cleared uses. This practice may be most common in patients with diseases for which there is no proven treatment, or in patients who have exhausted all approved/cleared treatments.”).

indication.¹¹⁵ The labeling may say that “because of marketing exclusivity” held by another company (and thus, presumably, for no other reason) the generic drug is “not labeled for pediatric use.” The labeling may even provide instructions for the indication in question—any “information” that FDA considers necessary for safe use. The labeling is, in short, noisy about the omitted new use. The agency has also started to implement noisy carve-outs in situations not authorized by this statutory provision. For instance, the labeling for Inflectra (infliximab-dyyb) omits pediatric ulcerative colitis, for which the innovator holds orphan exclusivity. Rather than merely approve partial labeling that omitted this use, FDA approved a noisy carve-out that effectively tells prescribers that Inflectra is safe and effective for the omitted (and protected) indication.¹¹⁶

B. *Impediments to Solving the Problem*

The factors just described work together to effect an end result that is inconsistent with the objectives of federal law. The law intends drug companies to have exclusive sales for the new uses they develop. But partial labeling to respect protected uses is functionally irrelevant when FDA deems a generic drug AB-rated to the innovator’s drug in the Orange Book, without regard for the scope of its approval. State pharmacy substitution laws and payer policies exacerbate the problem by authorizing or requiring the substitution of a therapeutically equivalent generic for the innovator’s drug, without regard for the scope of the generic drug’s approval. Thus, if the physician prescribes the innovator’s product for the new use, state law and payer policies will generally lead to dispensing of the generic product anyway. Even if state law and payer policies do not override the exclusivity, state law generally permits physicians to prescribe generic drugs and biosimilar biologics for any use, including an unapproved use, for which another company holds a patent or exclusivity. FDA will not interfere with this, considering it the practice of medicine. Indeed, the agency affirmatively undermines pediatric new-use patents and exclusivity by using noisy carve outs in generic and biosimilar labeling. The initial goal was for the innovator alone to enjoy sales

¹¹⁵ See 21 U.S.C. § 355a(o)(2) (2012). As explained above, FDA’s regulations permit generic drug labeling to omit an indication protected by patent or exclusivity, unless the generic drug would be less safe or effective than the innovator drug for the remaining, non-protected conditions of use. See 21 C.F.R. § 314.127(a)(7) (2017). Section 505A(o) authorizes an exception if the omitted information is pediatric information protected by three-year exclusivity, orphan exclusivity, or an extension of one of those exclusivities under a special provision for antibiotics. See 21 U.S.C. § 355(a)(o)(2). In this situation, FDA may approve the generic drug with the pediatric information omitted, *even if* the resulting labeling would make the generic drug less safe or effective.

¹¹⁶ See INFLECTRA PACKAGE INSERT § 8.4 (2016). Section 505A(o), which refers only to generic drug applications and not biosimilar applications, did not authorize this.

of the drug for the use in question. But in the end, the generic and biosimilar companies will take most of the sales.¹¹⁷

This problem cannot be solved through persuasion alone. Consider the challenge of persuading a physician to override substitution when prescribing an innovative drug for a newly approved use. Most state laws permit the physician to do so, for instance by writing “dispense as written” on the prescription form.¹¹⁸ But if FDA has deemed the generic drug therapeutically equivalent, the treating physician understands that as a clinical matter the two drugs are not distinguishable. She has no medical reason to write “dispense as written” on the prescription. Nor does the patient have any reason to insist on the innovative product, which may have a higher copayment. Even if the physician and patient know that the research in question needs to be paid for, and that further new-use innovations will be jeopardized unless patients receive and payers cover the innovator’s product for the protected new use, they are unlikely to select the more expensive of two clinically identical options. After all, doing nothing—acquiescing in the substitution that is the default in this situation—shifts the financial responsibility to another patient and payer. And if everyone behaves in this way, there is a classic tragedy of the commons: each acts according to his or her self-interest but contrary to the common good by spoiling the resource (here, the incentive for new-use research).

As a practical matter, it is exceptionally difficult for innovators to obtain judicial relief enforcing exclusivity in these situations. Public law appears to offer very little relief. The regulatory exclusivity provisions of the FDCA block FDA from approving other applications, and the agency avoids a violation by approving partial labeling. Regulatory exclusivity does not bind anyone other than the agency, so—for instance—it does not block a competitor

¹¹⁷ This is not an empirical claim; it is a structural point. Prescribers generally do not record medical conditions on prescriptions, and pharmacists and pharmacy benefit managers usually do not inquire about the patient’s condition. But substitution occurs automatically under state law. *See generally* PHARMACIST’S LETTER, STATE REGULATIONS ON GENERIC SUBSTITUTION (2009), <http://pharmacistsletter.therapeuticresearch.com/pl/ArticleDD.aspx?nidchk=1&cs=&s=PL&pt=2&fpt=2&dd=220901#CHART1186> (outlining laws governing the substitution of generics in each state). That is, if the prescription states the brand product, the pharmacy substitutes the generic. *See, e.g., id.* at 3 (noting that in Georgia, “[a] pharmacist may substitute a drug with the same generic name in the same strength, quantity, dose, and dosage form as the prescribed brand name drug product”). Unless there is reason to think that physicians, pharmacists, or payers step in to prevent generic substitution *specifically for protected uses*, if an innovator knows that fifty percent of the prescriptions for its product are for a particular indication, then fifty percent of the generic sales will be for that indication.

In rare cases, a new use may be associated with a new and tangible product feature—such as a new route of administration—that is itself protected by a patent or regulatory exclusivity. In these cases, the new use may be indirectly excludable, because the generic drug will not be approved in the particular physical form required.

¹¹⁸ *E.g.*, IND. CODE. 16-42-22-6 (2017).

from marketing or selling its product for the use.¹¹⁹ Nor does a new-use patent block FDA from approving a competitor's application for a drug that everyone understands will be dispensed for the protected use. If a generic company omits the use from its labeling, the patent has no bearing on FDA's authority to approve the generic drug.¹²⁰ The courts allow FDA to approve generic drugs with partial labeling even when the generic company realizes (and perhaps intends) that the vast majority of the sales will be infringing.

Private law solutions have not borne much fruit to date. As Professor Eisenberg explained in 2005, patent infringement cases face substantial challenges.¹²¹ Although a patent infringement suit is theoretically possible, the patient—a direct infringer—is not an appealing defendant.¹²² Nor is the physician or the payer. Although the physician might have direct liability, and both the physician and payer might face secondary liability, the innovator's

¹¹⁹ Other laws—including FDA's rules prohibiting promotion of an approved drug for an unapproved use—might prohibit the competitor from doing so. FDA proceeds against off-label promotion of prescription drugs using a complex theory that weaves together several statutory and regulatory provisions. Section 502(f)(1) of the FDCA deems a drug misbranded unless its labeling bears adequate directions for use. 21 U.S.C. § 352(f)(1). FDA interprets this to mean adequate directions for lay use, 21 C.F.R. § 201.5, which makes prescription drugs misbranded by default. Section 502(f)(1) allows FDA to exempt drugs from its provisions by regulation, however, and the agency has done so for prescription drugs. Section 201.100 of the agency's regulations exempts a prescription drug from section 502(f)(1) if, among other things, (1) the package insert bears "adequate information for its use" such that prescribers can use the drug for its intended purposes including all purposes for which the drug is advertised, and (2) if the drug is a new drug, this is the labeling approved with the new drug application. 21 C.F.R. § 201.100(c). Further, all labeling that discusses use of the drug—thus including written, printed, or graphic promotional pieces, *see* 21 U.S.C. § 321(m)—must provide adequate information for prescribers for all intended uses and advertised use, and all parts of that labeling must be "consistent with and not contrary to" the approved labeling. 21 C.F.R. § 201.100(d)(1). In addition, FDA's regulations also provide that the intended use of a drug can be based on labeling claims and advertising material, among other things, and also oral statements. 21 C.F.R. § 201.128. Finally, the FDCA defines a "new drug" as a drug that is not generally recognized as safe and effective for the conditions suggested in its labeling. 21 U.S.C. § 321(p). These statutory and regulatory provisions work together as follows. If the NDA holder promotes its drug for an unapproved use, it creates a new intended use. If the labeling does not contain adequate information about that use, then the manufacturer violates section 201.100 of FDA's regulations. If it violates section 201.100, then it no longer qualifies for the exemption from section 502(f)(1) of the FDCA, and its drug is misbranded. If the company instead unilaterally changes its labeling to provide information about the use, then it also turns its product into an unapproved new drug with respect to that use.

¹²⁰ If the generic company wants to *include* the new use in its labeling, the statute *does* block FDA from approving the generic drug. 21 U.S.C. § 355(j)(5)(B) (2012) (delaying approval of a generic application if the applicant chooses to wait for expiry of a new-use patent or challenge a new-patent, but not if the applicant chooses to omit the patented use from its labeling); *id.* § 355(j)(2)(A)(viii) (allowing generic applicant to omit a patented use from its labeling by providing a "section viii" statement to the patent owner). In contrast, new-use patents never affect FDA's authority to approve biosimilar biologics. There is no statutory link between a biologic innovator's patents and FDA's authority to approve biosimilar or interchangeable biologics. *See* Lietzan, *supra* note 4, at 933–34.

¹²¹ *See* Eisenberg, *supra* note 7, at 724; Roin, *supra* note 7, at 36 n.258.

¹²² In this context direct infringement means *using* the patented invention. 35 U.S.C. § 271(a) (2012). The patient might infringe directly by taking the medicine for the patented use.

success in the marketplace depends on prescriptions from physicians and contracts with payers.¹²³ Under current law, it can be very hard to establish that a generic company induced infringement of a patent claiming a protected use omitted from the labeling. The statute specifies liability if the generic company “actively” induced infringement. But the Hatch–Waxman scheme for generic drug approval ensures that most patent litigation against generic companies occurs prior to generic drug launch.¹²⁴ In this prelaunch scenario, knowledge that a generic drug will be dispensed for an unapproved use, and even intent that it be dispensed for the use, are usually not enough to show

¹²³ Depending on how the claims were drafted, a physician might directly infringe by administering the drug for the patented use.

Secondary liability for healthcare professionals and the payer would presumably be grounded in induced infringement. See 35 U.S.C. § 271(b) (“Whoever actively induces infringement of a patent shall be liable as an infringer.”) For instance, a physician might infringe by providing instructions to the patient to use the generic drug in a way that infringed the innovator’s patent. A pharmacist might infringe by dispensing a generic drug for a patient’s infringing use, with instructions for that use. A payer might infringe by steering its covered patients to approved generic drugs with labeling carve-outs, through a blanket substitution requirement and preferential co-payments. See *Takeda Pharm. U.S.A., Inc. v. West-Ward Pharm. Corp.*, 785 F.3d 625, 630–31 (Fed. Cir. 2015) (noting that inducement can be found if there is “[c]vidence of active steps taken to encourage direct infringement,” such as “instructing how to engage in an infringing use” (quoting *Metro-Goldwyn-Mayer Studios Inc. v. Grokster, Ltd.*, 545 U.S. 913, 936 (2005)) (alteration in original)).

But inducement theories face challenges. Although section 271(b) does not refer to the inducer’s knowledge or purpose, U.S. courts generally require some degree of knowledge and intent. How much they do (and should) require remains unclear and disputed. *E.g.*, *Warner-Lambert Co. v. Apotex Corp.*, 316 F.3d 1348, 1364 (Fed. Cir. 2003) (“[S]pecific intent and action to induce infringement must be proven.”); see also Mark A. Lemley, *Inducing Patent Infringement*, 39 U.C. DAVIS L. REV. 225, 226 (2005) (“[T]he actual requirements for inducement liability have remained something of mystery.”).

As a practical matter, pharmaceutical patent owners do not sue physicians, pharmacists, or payers for induced infringement; they sue generic companies. See Brief for AbbVie Inc. as Amicus Curiae in Support of Petitioner at 2, *Commil USA, LLC v. Cisco Systems, Inc.*, 135 S. Ct. 1920 (2015) (No. 13-896) (“But it is impossible, as a practical matter, to enforce [method of use] patents by suing for direct infringement. After all, the only people who actually use Compound X to treat Disease Y are doctors and patients. But it would be both impractical and contrary to public policy for pharmaceutical companies to sue thousands of doctors and patients individually.”). As a result, there is very little judicial discussion of induced infringement theory with respect to these other market participants—and even less scholarship. Recent developments in Europe could invigorate the discussion. In November 2017 the Dutch Supreme Court held that a company could be liable for induced infringement of a new-use patent if the infringing use is foreseeable—that is, if it offers or delivers the generic drug to people who *lack a license to use the drug in this way, if it knows or it should be obvious under the circumstances that the drug is suitable for and will be used for the patented use*. HR 3 Nov. 2017, *RvdW 2017, 1170 ¶¶ 3.6.1–3.6.6* (*Merck Sharp & Dohme Corp./Teva*) (*Neth.*), <https://uitspraken.rechtspraak.nl/inziendocument?id=ECLI:NL:HR:2017:2807>; *Bert Oosting et al., Dutch Supreme Court Hands Down Landmark Decision on Infringement of Second Medical Use Patents*, *LIMEGREEN IP NEWS* (Nov. 13, 2017).

¹²⁴ The Hatch–Waxman Amendments created an artificial act of direct infringement—submission of a generic drug application seeking permission to market the drug during the term of an unexpired patent. 35 U.S.C. § 271(c)(2)(A) (2012). This creates federal court jurisdiction for the patent infringement case prior to FDA approval and market launch.

active inducement.¹²⁵ An induced infringement claim in the postlaunch setting currently requires not only proof of direct infringement, but also proof that the generic company took affirmative actions intended to cause this direct infringement and proof that the inducement (instead of other factors) caused the direct infringement.¹²⁶ Successful cases are rare.¹²⁷ In an exceptional case, the innovator might be able to invoke a contributory infringement theory, but the statute permits recovery only if the generic drug is not suitable for substantial noninfringing use.¹²⁸

More work could be done on solutions to the new-use problem using currently available legal doctrines. For example, if a generic or biosimilar company obtained approval of its product on the basis of an innovator's marketing application and then courted sales of its product for a use still protected by the innovator's regulatory exclusivity, there might be room for arguments grounded in misappropriation, conversion, or unfair competition.¹²⁹ It may also be worth considering whether state laws are preempted when they require substitution of generic drugs that, when substituted, lead to infringement of patents issued by the federal government.¹³⁰ These theories have not been fully explored to date by litigants or, indeed, by scholars.

¹²⁵ *E.g.*, Warner-Lambert Co. v. Apotex Corp., 316 F.3d 1348, 1364–65 (Fed. Cir. 2003) (finding no infringement under 35 U.S.C. § 271(e)(2) when asserted patent was for a use for which the generic drug was not approved, also finding no inducement under § 271(b) before launch because there was no evidence the generic company would encourage or promote doctors to prescribe, or pharmacists to dispense, its drug in a manner that would infringe the patent).

¹²⁶ *E.g.*, Final Jury Instructions at 26, GlaxoSmithKline LLC v. Teva Pharm. USA, Inc., 313 F.Supp.3d 582 (D. Del. Mar. 8, 2018) (No. 14-878-LPS-CJB).

¹²⁷ In a rare example, Teva was ordered to pay GlaxoSmithKline \$235 million for inducing infringement of a use patent covering Coreg (carvedilol). Jury Verdict at 8, GlaxoSmithKline LLC v. Teva Pharm. USA Inc., 313 F.Supp.3d 582 (D. Del. Mar. 8, 2018) (No. 14-878-LPS-CJB); Nate Raymond, *GSK Wins \$235 million from Teva in Coreg Patent Trial*, REUTERS (June 21, 2017, 6:53 PM), <https://www.reuters.com/article/us-gsk-teva-pharm-ind-idUSKBN19C32B>. The court later entered judgment as a matter of law for the defendant, on the theory that GSK failed to prove Teva's actions, as opposed to other factors, caused the physicians to directly infringe the patent. Memorandum Opinion at 2, GlaxoSmithKline LLC v. Teva Pharmaceuticals USA Inc., 313 F.Supp.3d 582 (D. Del. Mar. 8, 2018) (No. 14-878-LPS-CJB). GlaxoSmithKline has appealed.

¹²⁸ 35 U.S.C. § 271(c) (2012).

¹²⁹ For example, Amgen alleged conversion under California law, when Sandoz filed a biosimilar application citing Amgen's biologics license but declined to participate in the premarket patent information exchange specified in federal law for biosimilar applicants. *See* Amgen v. Sandoz, 794 F.3d 1347, 1352–53 (Fed. Cir. 2015). The trial court dismissed this claim on the theory that the statute permitted Sandoz to decline participation. *Id.* at 1350–51. Neither the Federal Circuit nor the Supreme Court considered the conversion theory.

¹³⁰ *E.g.*, Biotechnology Indus. Org. v. District of Columbia, 496 F.3d 1362, 1374 (Fed. Cir. 2007) (finding the District of Columbia Prescription Drug Excessive Pricing Act preempted by federal patent law, because it struck a different balance—from the one set by Congress—with respect to exclusionary power, length of patent term, and conditions of patentability and thus rebalanced exclusion and free use). The author is grateful to Professor Sarnoff for reminding her of this case.

IV. POTENTIAL SOLUTIONS

Federal law is designed to provide a temporary period of exclusive sales for new uses. Yet innovators who develop new uses protected by patent and exclusivity do not enjoy exclusive sales.¹³¹ The problem is not that the patent and regulatory exclusivity statutes are poorly drafted. Generic drugs are dispensed for infringing uses because FDA designates them AB-rated, because state laws and payers require or strongly encourage their substitution, and because physicians are unlikely to write “dispense as written” when prescribing an innovative product for a new use (even if they have good reason to suspect the new use is protected). Biosimilar biologics may also be dispensed for unapproved protected uses when physicians prescribe them for those uses, or when payers require their dispensing for those uses, and interchangeable biologics are likely to be substituted for protected uses just as generic drugs currently are. The problem stems from a combination of rules, practices, and policies in the broader regulatory approval, drug distribution, and healthcare financing systems.

It is widely understood that these sales happen and that the sales are flatly contrary to the intent of federal law. We have simply acquiesced to a healthcare system in which they occur as a matter of course.¹³² But the sales need to stop if the federal laws in question are to have any meaning. The subsections that follow describe steps policymakers could take. They recognize that we have a profound interest in the prompt approval and seamless substitution of generic equivalents for compounds and uses that are no longer protected by patent or regulatory exclusivity. We also have a profound interest in ensuring that physicians may prescribe approved medicines for unapproved and novel uses when, in their clinical judgment, doing so is in the best interest of their patients. This part therefore assumes that any solution to the problem described in Part III must achieve three objectives; it must: (1) eliminate infringing sales and uses; (2) permit approval and facilitate substitution

¹³¹ Although this Article focuses on innovators continuing to study their own approved drugs for new uses, one company repurposing another company’s drug for a new use will face a similar problem. A physician might prescribe the original innovative product, even if that product is not approved for the use. If generic substitutes are available, the pharmacist might substitute the generic version of the original innovative product, even though it too is not approved for the use. The second innovator may never enjoy the sale.

¹³² Policy discussions and policymakers frequently ignore this rampant disregard for federal law. For instance, the Department of Health and Human Services calculates generic drug utilization rates by comparing the number of A-rated generic drugs dispensed with the number of prescriptions written. *See, e.g.*, DEP’T OF HEALTH AND HUMAN SERVS., OFFICE OF INSPECTOR GEN., *GENERIC DRUG UTILIZATION IN THE MEDICARE PART D PROGRAM* 9 (2007), at 9. The policy discussion relating to generic utilization rates and the savings that can be achieved with generic drugs is utterly divorced from the possibility that some of those sales are for unapproved uses for which an innovator holds a patent or exclusivity. No one would dispute that increasing lawful generic drug utilization contributes to the public welfare by reducing healthcare costs. But when policymakers, researchers, and others include infringing sales in a highly touted utilization rate, they endorse and implicitly encourage those sales.

of generic drugs for unprotected compounds and unprotected uses; and (3) permit physicians to engage in clinically motivated off-label prescribing.

A. *Changes in Administrative Practices and Policies*

To begin with, FDA should change its practices and policies that contribute to the problem. None of these practices or policies are essential to ensuring appropriate generic approvals and substitution. Because the underlying goal—ensuring that the innovator, alone, captures sales for the excludable new use, as intended by Congress—is sound, the changes described below should not be controversial, even if some of them would represent radical changes in how the agency operates.

1. Revisions to the Orange Book

First, FDA should revise its approach to therapeutic equivalence ratings in the Orange Book. This would be feasible without a change in the statute.¹³³ For instance, the agency could limit therapeutic equivalence determinations to generic drugs with labeling identical to their reference products, except for editorial differences stemming from the fact that the two drugs are produced or distributed by different manufacturers. This would, however, be controversial. Some generic drugs currently deemed therapeutically equivalent would lose those ratings. And with this new policy in place, generic drugs might receive and then lose these ratings (if the innovators obtained approval of new uses). More significantly, this approach—though perhaps the simplest

¹³³ As noted earlier, *supra* Section III.A., FDA created the Orange Book and invented therapeutic equivalence ratings on its own initiative. The statute does not mention them. See generally 35 U.S.C. § 271. Although the agency could make changes to the Orange Book without legislative action, it should—and almost certainly would—provide notice and solicit comment. FDA initially planned no administrative proceedings when it constructed the Orange Book in 1979 and 1980. See *Pharm. Mfrs. Ass'n v. Kennedy*, 471 F. Supp. 1224, 1225–26 (D. Md. 1979). After the research-based industry brought suit challenging the agency's statutory authority to issue the publication and the lack of administrative procedures, FDA opted to conduct notice and comment rulemaking. *Id.* at 1226. The court, however, never reached the merits of the procedural claim. See *id.* at 1227. Many years later, the agency rejected an argument that it was required to use rulemaking before issuing therapeutic equivalence ratings for drugs approved under section 505(b)(2), which is different from the generic drug provision. See Dep't of Health & Human Services, Letter to Dan Himmelfarb, Philip Katz, and Benjamin Del Tito Re: Docket Nos. FDA-2011-P-0610 and FDA-2013-P-0371 3 (July 23, 2014). FDA reasoned in part that therapeutic equivalence determinations are not binding and have no legal effect. *Id.* at 15. FDA may well be correct that incorporation of its advice into laws that are not administered by the agency (i.e., state pharmacy law) does not make the advice binding for purposes of determining whether the Administrative Procedure Act requires rulemaking. The changes described in the text would have a significant impact on regulated industry, and as a practical matter FDA would probably choose a public procedure, particularly as it considered how to apply the changes to drugs already listed in the Orange Book.

change for FDA to make to the Orange Book—would fail the test specified at the outset of this discussion. It would defeat automatic substitution for compounds and uses that are no longer protected. Any solution adopted must preserve automatic substitution of approved generics for compounds and uses that are not protected by patent or exclusivity.

To help ensure that a generic drug would still be substituted automatically for older unprotected uses, though, FDA could explore a rating system that communicated partial therapeutic equivalence and full therapeutic equivalence. One approach might be a special annotation to the AB rating to indicate that the generic drug does not yet have the full scope of approval or (therefore) therapeutic equivalence. A handful of drugs already have three-letter ratings (AB1, AB2, and so forth), so another approach (such as AB-L, for limited) would be necessary.¹³⁴ Another approach would be to assign therapeutic equivalence on an indication-by-indication basis, which would require listing indications separately in the Orange Book. Regardless of the changes made to the Orange Book, implementation (particularly re-rating all generic drugs on the market today, under the new system) would be burdensome for the agency, and the transition could be confusing to participants in the healthcare system.

A broader philosophical objection to these suggestions would be that therapeutic equivalence is a scientific and clinical concept, not a legal or regulatory concept. As a scientific matter, a generic drug that has the same strength and is bioequivalent should produce the same clinical result in any given patient, and this is true even with respect to uses for which the innovator's product is not yet approved. In other words, some will feel that it is disingenuous to suggest the generic drug is not therapeutically equivalent for a particular use when, in fact, as a clinical matter, the drug is. The answer is that FDA would have to recast what it is doing when it provides an AB rating in the first instance. The Orange Book begins with a 20-page article describing the history and purpose of therapeutic equivalence determinations and explaining the codes.¹³⁵ It is long past time for the agency to discuss in this preface the significance of partial labeling and the importance of preserving incentives for new-use innovation. FDA could explain that the AB rating reflects more than just a judgment about expected clinical results; it also takes

¹³⁴ FDA assigns three-character codes when there is more than one reference listed drug with the same active ingredient and strength, and the drugs are not bioequivalent to each other. For example, Alvogon holds an NDA for Adalat CC (nifedipine), and Pfizer holds an NDA for Procardia XL (nifedipine). These are independently developed drugs and not bioequivalent to each other. Generic drugs therapeutically equivalent to Adalat CC receive an AB1 rating, and generic drugs therapeutically equivalent to Procardia XL receive an AB2 rating. See 38TH ORANGE BOOK, *supra* note 93, at xv–xvi.

¹³⁵ 38TH ORANGE BOOK, *supra* note 93, at iv–xxv.

account of domestic innovation policy and new-use incentives that the agency itself is partially responsible for enforcing.¹³⁶

Another objection might be that restructuring the therapeutic equivalence system will not meaningfully stem the tide of infringing uses. This is a fair criticism. State laws vary. Some refer to substituting another drug with the “same active ingredient,” for instance, and others refer to substituting a “generic” drug.¹³⁷ Surprisingly few reference a “therapeutic equivalence” determination by FDA, let alone an “AB” rating.¹³⁸ Thus changes in the Orange Book might not lead to a different result under the pharmacy laws of many states. And in other states, even if FDA’s changes prevented automatic substitution for infringing uses, a payer might nevertheless require use of the generic drug (or steer patients toward the generic drug by accepting a lower co-payment), without regard to the scope of its approval, the nature of the patient’s condition, or the scope of FDA’s therapeutic equivalence determination. Without a strategy that *also* changes payer (or pharmacist, or prescriber) practices, a refashioned Orange Book is therefore only a partial solution. But as Part III illustrated, at least part of the problem is automatic substitution under blanket AB ratings. And it is hard to conceive of a solution involving payers, pharmacists, and prescribers that does not require greater transparency across the board about the scope of each generic drug’s approval. FDA has the last word on the scope of a drug’s approval, and it is the best positioned to maintain easily accessible databases about approved drugs—and the scope of their approval—for healthcare professionals and payers.

Moreover, it is not crazy to suggest the Orange Book be overhauled. As noted, the publication is dated, and some of its policies may not be entirely rational. There is room to wonder, for instance, why a 20 mg capsule should not be rated therapeutically equivalent to a 20 mg tablet if in fact the two are bioequivalent. Under the agency’s current approach, they are not deemed substitutable—which has led to ridiculous generic company strategies, like

¹³⁶ FDA should also re-insert in the Orange Book the statement that it does not provide therapeutic equivalence determinations for unapproved uses. This should not be controversial, but it also would not have much impact standing alone.

¹³⁷ *E.g.*, ALASKA ADMIN. CODE tit. 12, § 52.510(b) (2018); ALASKA STAT. § 08.80.480(11) (2017) (permitting substitution only if the drug has the same established name, active ingredient, route of administration, dosage form, and strength); CONN. GEN. STAT. ANN. § 20-619(b) (West 2017) (permitting substitution of a “generic drug product with the same strength, quantity, dose and dosage form . . . which is, in the pharmacist’s professional opinion, therapeutically equivalent”); MINN. STAT. § 151.21 (2018) (prohibiting substitution of a generically equivalent drug “unless, in the pharmacist’s professional judgment, the substituted drug is therapeutically equivalent and interchangeable to the prescribed drug”).

¹³⁸ For examples that do, see ARK. CODE ANN. § 17-92-503(c) (2018); Ark. Bd. of Pharm. Regulation 07-00-0006 (2014) (permitting a pharmacist to substitute only A-rated drugs); MISS. CODE ANN. § 73-21-73(m) (2017) (defining “generic equivalent drug product” to include any drug listed by FDA as therapeutically equivalent); S.D. CODIFIED LAWS § 36-11-2(13) (2017) (defining an “equivalent drug product” as one deemed therapeutically equivalent in the latest edition of the Orange Book).

placing tablets inside capsules.¹³⁹ FDA may soon start issuing interchangeability ratings for biological products, and these will be added to the “Purple Book,” a document on the agency’s website that lists licensed biologics and biosimilars.¹⁴⁰ The agency has recently asked for input on the information that it should include in the redesigned Purple Book,¹⁴¹ which provides a good opportunity for a redesign of the corresponding drug book or, perhaps, integration of the two into one database. Whatever FDA does with the Orange Book and Purple Book, it would need to make conforming changes to the Drugs@FDA website,¹⁴² which also lists therapeutic equivalents for each approved drug.

2. Regulation of Generic Drug Promotion

Second, FDA should prohibit a drug company from discussing an unapproved use with healthcare professionals or payers if the use is protected by another company’s patent or regulatory exclusivity. The agency has historically taken the position that promotion of an approved drug for an unapproved use renders the drug misbranded (and in some cases an unapproved new drug).¹⁴³ A series of First Amendment cases has prompted FDA to review its regulations and policies governing medical product communications, and as part of this exercise it could take the opportunity to state that companies may not discuss unapproved and infringing uses of their drugs.¹⁴⁴

¹³⁹ For instance, Mylan Pharmaceuticals tucked its 100-milligram generic phenytoin tablet into a capsule, in order to receive a rating of therapeutic equivalence to Dilantin (phenytoin), which was marketed in capsule form. *See Warner-Lambert Co. v. Shalala*, 202 F.3d 326, 328 (D.C. Cir. 2000) (affirming FDA’s decision to find therapeutic equivalence).

¹⁴⁰ *See generally* FDA, Purple Book: Lists of Licensed Biological Products with Reference Product Exclusivity and Biosimilarity or Interchangeability Evaluations, <https://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/ucm411418.htm> (last visited Aug. 31, 2018).

¹⁴¹ *See* HHS Blueprint to Lower Drug Prices and Reduce Out-of-Pocket Costs, 83 Fed. Reg. 22,692, 22,696 (May 16, 2018) (“How could the Purple Book be more useful to health care professionals, patients, manufacturers, and other stakeholders? What additional information could be added to increase the utility of the Purple Book?”).

¹⁴² Drugs@FDA is a portal through which one can access basic information and documents on approved new drugs and biological products, frequently including approval letters and agency review documents. *See Drugs@FDA Database*, <https://www.fda.gov/Drugs/InformationOnDrugs/ucm135821.htm> (last visited Oct. 8, 2018). For each listed product, there is a drop-down menu labeled “Therapeutic Equivalents.” *See, e.g., Activase*, DRUGS@FDA: FDA APPROVED DRUG PRODUCTS, <https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.proccss&ApplNo=103172> (last visited Oct. 8, 2018).

¹⁴³ *See* Nathan Cortez, *The Statutory Case Against Off-Label Promotion*, 83 U. CHI. L. REV. ONLINE 124, 129–33 (2016) (explaining theory).

¹⁴⁴ *See, e.g., United States v. Caronia*, 703 F.3d 149, 169 (2d Cir. 2012) (concluding that the prosecution of a sales representative marketing Xyrem (sodium oxybate) for off-label uses violated his first amendment rights); *Amarin Pharma, Inc. v. FDA*, 119 F. Supp. 3d 196, 237 (S.D.N.Y. 2015) (granting manufacturer’s motion for preliminary injunction in case alleging violation of first amendment rights).

Although any such prohibition would need to be squared with First Amendment principles, precluding discussion of unapproved uses protected by patent or regulatory exclusivity would presumably directly advance the government's substantial interest in preserving incentives for innovation.¹⁴⁵ FDA appears to agree, noting that promotion of approved drugs for unapproved uses "protected by patents or exclusivity held by another applicant . . . would undermine these incentives for innovation."¹⁴⁶

If the agency does not change its basic approach to AB ratings in the Orange Book, it should resurrect its abandoned guidance governing promotion by generic drug companies and, in that guidance, expressly prohibit statements that a generic drug is equivalent, therapeutically equivalent, or AB-rated if the drug is not approved for the same uses as the innovative drug, *unless* the company also provides its labeling and points out in the same communication that its drug is neither approved for, nor AB-rated for, all of the uses. To be sure, generic companies usually do not promote their drugs, apart from in press releases, on their websites, and in price catalogs distributed to payers. But typically, these catalogs identify the corresponding innovative drug and indicate whether the generic drug is AB-rated. FDA should require full transparency in these documents about the scope of the generic drug's approval.

This suggestion does not require a significant departure from current advertising and promotion rules. Promotional pieces about a drug must provide information about the drug's approved uses in the same language as in the approved package insert,¹⁴⁷ and industry practice is to provide the approved labeling at the same time. "'Reminder' labeling[,] which [just] calls attention to the name of the drug" and (if desired) the price, is exempt from this requirement.¹⁴⁸ If a piece suggests the drug's use, however, it is not reminder labeling, and FDA takes the view that comparing one drug to another implies the drug's uses.¹⁴⁹ This is why FDA issued draft guidance in 1994

based on threatened enforcement action for promotion of a drug for an off-label use). The FDA has released several draft and final guidance documents as a part of this process. *See, e.g.*, FDA, MEDICAL PRODUCT COMMUNICATIONS THAT ARE CONSISTENT WITH THE FDA-REQUIRED LABELING: QUESTIONS AND ANSWERS 1 (2018).

¹⁴⁵ *See* Cent. Hudson Gas & Elec. Corp. v. Pub. Serv. Comm'n of New York, 447 U.S. 557, 566 (1980) (laying out test for constitutionality of commercial speech restrictions which includes whether the restriction directly advances a substantial government interest); *e.g.*, U.S. Const. Art. I, § 1, cl. 8 (granting Congress the power "[t]o promote the Progress of . . . useful Arts, by securing for limited Times to . . . Inventors the exclusive Right to their respective . . . Discoveries"); Exec. Order No. 13,731, 81 Fed. Reg. 42,221 (June 24, 2016) (noting that "[i]t is in the national interest for the Federal Government to support innovation").

¹⁴⁶ *See* FDA, MEMORANDUM: PUBLIC HEALTH INTERESTS, *supra* note 114, at 16.

¹⁴⁷ *See* 21 C.F.R. § 201.100(c)(1) (2017).

¹⁴⁸ *Id.* § 201.100(f).

¹⁴⁹ *E.g.*, FDA, *Reminder Advertisements and Labeling*, OPDP FREQUENTLY ASKED QUESTIONS (FAQs), <https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm090308.htm#ReminderAdvertisementsandLabeling> (last visited Aug. 18, 2018).

explaining that statements in labeling and advertising that a generic drug is equivalent, bioequivalent, or AB-rated “take the promotional material out of the reminder labeling or advertising exemption.”¹⁵⁰ The agency said it would exercise enforcement discretion with respect to the requirement to include the full labeling in the case of a price catalog listing the generic manufacturer’s entire product line with bioequivalence codes.¹⁵¹ But it did not announce enforcement discretion with respect to any other provisions of law, such as the rule that the labeling may not be false or misleading, including misleading by omission.¹⁵²

FDA withdrew the guidance in 1997, announcing plans to issue a new guidance on generic drug promotion that further explored the use of the term “A-rated” in promotional materials.¹⁵³ More than twenty years have passed, and it appears the agency has not yet issued the guidance in question. As part of its review of the regulation of medical product communications, FDA could revive this guidance. To affirm its commitment to the statutory incentives for new-use innovation, the agency could reaffirm the position that it took in 1994 and decline to exercise enforcement discretion. Thus, any statements about AB rating would need to be accompanied by the generic drug’s approved labeling—which would show the scope of the drug’s approval.

FDA could take an even more aggressive stance, explaining that if: (1) a generic company promotes its drug as “A-rated” when the drug is not approved for all of the innovator’s indications, all of the innovator’s indications are “intended uses” of the generic drug in question; and (2) a generic company disseminates promotional pieces stating that its product is “AB rated” in this situation, the labeling in question is misleading by omission. This would need to be supported by clarification in the Orange Book that AB ratings apply only to approved uses. These theories would, operating together, render the generic drug misbranded under section 502 of the FDCA, which in turn would mean the generic companies with partial labeling could not make those statements.¹⁵⁴ The agency could also prioritize enforcement action against generic drug companies that promote their approved generic

¹⁵⁰ FDA Letter to Industry, Current Issues and Procedures (April 1994).

¹⁵¹ *Id.*

¹⁵² *Id.*; see also 21 U.S.C. §§ 321(n), 352(a) (2012).

¹⁵³ See Prescription Drug Advertising and Promotional Labeling; Development and Use of FDA Guidance Documents; Request for Comments, 62 Fed. Reg. 14,912, 14,916 (Mar. 28, 1997).

¹⁵⁴ First, if a drug has an intended use for which it is not approved, then its approved labeling will lack adequate information for prescribers for that use, rendering the drug out of compliance with 21 C.F.R. § 201.100 (2017). Prescription drugs in compliance with section 201.100 receive an exemption from section 502(f)(1) of the FDCA, which would otherwise deem them misbranded for lacking adequate directions for (lay) use. See 21 C.F.R. § 201.5 (explaining that “[a]dequate directions for use” means adequate directions for lay use, which means that prescription drugs are inherently misbranded under section 502(f)(1) and must qualify for the exemption in 21 C.F.R. § 201.100). Second, section 502(a) deems a drug misbranded if its labeling is false or misleading in any particular, and section 201(n) adds that labeling may be misleading if it fails to reveal facts that are material in light of the representations made or material in view of the consequences resulting from use.

drugs for unapproved uses, whether directly or through reference to AB ratings.

But these steps, too, are partial solutions. If state law and payer practices remain the same, cabining promotion by generic companies will help only around the margins. Again, though, a solution involving payers, pharmacists, and prescribers will inherently require greater transparency across the board about the scope of each generic drug's approval. The suggestions in the preceding paragraphs should not be controversial. They aim to ensure that generic companies—like FDA—take reasonable steps to ensure that accurate and full information about the approval of their drugs flows to all relevant participants in the healthcare system.

3. Education about New-Use Protections and Partial Labeling

FDA should educate participants in the healthcare system about the importance of new-use protections and the meaning of partial labeling. As noted already, the agency should more prominently discuss the significance of partial labeling in the Orange Book. It would also be helpful for FDA to restate the purpose of its practice of medicine policy, confirming that the policy does not describe situations in which a physician prescribes or administers a generic or biosimilar for an unapproved use for which another company holds a patent or regulatory exclusivity. Clarifying the purpose of the practice of medicine policy could be part of a broader signal to the healthcare community that society has a profound interest in maintaining statutory incentives to develop new uses. Although likely more controversial, FDA could require drug companies with partial labeling to include “Dear Pharmacist” (and “Dear Doctor”) letters with every shipment, stating that: (1) the product in question is not approved for every indication and therefore not AB rated for every indication; (2) unlabeled uses may be protected by patent and/or exclusivity held by another company; and (3) selling or using the product for these protected uses would be inconsistent with federal law and may expose the seller or user to liability. This would not be burdensome; as noted, drug companies are already required to include labeling with every shipment.¹⁵⁵

4. Refraining from Encouraging Infringing Uses

It should go without saying that agency staff should not publicly disseminate information about the safety and effectiveness of infringing uses of generic drugs and biosimilars. With the narrow exception of noisy carve-outs that Congress has authorized, no generic drug labeling should suggest or

¹⁵⁵ 21 C.F.R. § 201.100(c)(1).

imply a use for which the drug is not approved.¹⁵⁶ No biosimilar labeling should suggest or imply a use for which the biosimilar is not approved.¹⁵⁷ And FDA officials should not publicly vouch for the safety and effectiveness of a generic drug or biosimilar biologic for patented or exclusivity-protected uses that the company does not seek for the product's labeling.¹⁵⁸ The agency's affirmative contribution to the problem, however small the contribution might be in practice, must stop.

B. *Action-Forcing Legislative Steps*

To stop infringing sales and uses, federal or state legislative action might be needed. Each of the three ideas below places the burden on a different entity in the healthcare delivery system. The goal in each case is to prompt adoption of a private solution—which would probably involve indication-based prescribing, dispensing, and pricing—that will put an end to infringing sales and uses while preserving the sale and use of generic drugs for off-patent and unprotected uses.

1. Pharmacists

First, Congress could prohibit pharmacists from dispensing a generic drug or biosimilar drug for a protected use that does not appear in its labeling. Although pharmacy regulations are usually a matter of state law, there is some precedent for handling this at the federal level. It is currently an act of

¹⁵⁶ FDA's regulations already prohibit any statements in labeling that suggest or imply an off-label use. *E.g.*, 21 C.F.R. § 201.57(c)(2)(iv) (stating that for drugs, "[i]ndications or uses must not be implied or suggested in other sections of the labeling if not included in this [Indications] section."); *id.* § 201.57(c)(2)(v) (similar rule for biological products). Noisy carve-outs are inconsistent with this regulation. Congress has authorized noisy carve-outs for new pediatric uses in narrow circumstances, *see supra* Section III.A, but this effectively voids the patents and exclusivity protecting those uses and should be reconsidered.

¹⁵⁷ Again, FDA's regulations already prohibit this. *See supra* note 156.

¹⁵⁸ And yet they do so. For instance, in connection with its February 2016 advisory committee meeting considering the biosimilar Inflectra (infliximab-dyyb), FDA openly discussed use of the biosimilar for pediatric ulcerative colitis, even though the innovator held orphan exclusivity protecting the indication until September 2018. *E.g.*, FDA, BRIEFING DOCUMENT: ARTHRITIS ADVISORY COMMITTEE MEETING, BLA 125544 7, 10 (2016). Further, even though it did not ask committee members to vote on licensure for the indication, it asked their views on the product's biosimilarity for the indication. *Id.* at 12. *See also* FDA, TRANSCRIPT, ARTHRITIS ADVISORY COMMITTEE 217 (2016) (presenting agency's view that similar pharmacokinetics and bio-distribution would be expected for pediatric ulcerative colitis); *id.* at 331–32 (explaining that final discussion topic will be whether there is sufficient scientific justification to support a determination of biosimilarity for pediatric ulcerative colitis); *id.* at 389–413 (committee discussion of various indications including pediatric ulcerative colitis). A spokesperson for the National Organization for Rare Disorders objected to FDA's decision to discuss the indication. *Id.* at 309–11.

“misbranding” under the FDCA for a pharmacist to dispense a prescription drug without an effective oral or written prescription.¹⁵⁹ Congress could similarly deem it an act of misbranding to dispense a generic drug or biosimilar biologic for a use for which the product lacks adequate directions (which would effectively mean an unlabeled use) if the information was carved out due to another company’s patent or exclusivity.¹⁶⁰ Of course, a pharmacist would need to know the planned use of the drug for this to work. But if this were made law and FDA indicated plans to enforce the provision (perhaps with a mandate to do so and enhanced penalty provisions), then presumably pharmacists would be motivated to work with other parties in the healthcare delivery and finance system to ensure that the necessary information was provided. For instance, pharmacists might refuse to substitute generic drugs with partial labeling without assurances that the prescriptions fell within their labeling.¹⁶¹ This refusal would inform contract negotiations between pharmacies and payers and between pharmacies and generic drug companies. Payers might be motivated to switch to a system in which every reimbursed generic drug sale required a diagnosis that corresponded to the drug’s labeling.¹⁶²

Without a doubt, pharmacists would oppose this proposal. But placing the burden on pharmacists is appealing for the simple reason that they are in the best position to avoid an infringing sale and use. The pharmacist knows which generic drug might be dispensed to a particular patient. And the pharmacist has a copy of the professional labeling for the generic drug in question, because federal law requires that the labeling be shipped with the drug. Still, pharmacists might be concerned about the judgment calls necessary under this model. For instance, if two indications (one in the labeling, and one carved out) were similar but not identical, and if the patient’s condition did not fit squarely within either, it might be difficult for the pharmacist to determine whether the patient’s use was the carved-out use. Perhaps contractual negotiations between pharmacists and payers would place the risk on the payer in these situations. In other instances, a protected new use might not correspond directly to an approved indication statement, which could make it hard for a pharmacist to determine whether treatment of the patient falls within the carved-out use. This could be addressed by limiting the new misbranding provision to “new indications,” rather than the broader “new uses,” but it could also be addressed privately through payers assuming the risk.

Something similar could instead be done at the state level. That is, the states could amend their pharmacy laws to require that, if a generic drug or

¹⁵⁹ 21 U.S.C. § 353(b)(1) (2012).

¹⁶⁰ This should apply only if the innovator holds a patent or exclusivity. If it applied more broadly, it would frustrate traditional off-label prescribing. FDA, which has enforcement responsibility for the misbranding provision and for the approval of labeling, will know whether the use in question was carved out for reasons of patent or exclusivity. See *supra* Section III.A.

¹⁶¹ There might be preemption issues to sort through, particularly if state law required substitution.

¹⁶² Payers already collect information about a patient’s condition and the planned use of a medicine, when they subject a drug or biologic to “prior authorization” requirements. Roin, *supra* note 7, at 58–65.

biosimilar has partial labeling due to regulatory exclusivity or patent protection, the pharmacist verify that the patient's condition is a labeled use before dispensing the product. It would, however, be difficult to persuade every state's legislature to act. Each would have to agree to enact legislation bolstering federal intellectual property policy at considerable expense to its own budget. Even if every state could be persuaded to act, which seems improbable, uniformity in approach would be unlikely. Because the issue is ultimately a matter of national innovation policy, it seems a better fit for federal rather than state legislation.

2. Payers

Second, Congress might focus on payers. Professor Roin suggests a model in which pharmaceutical companies require payment from health insurers for infringing sales.¹⁶³ He views the problem of new uses as an information problem and argues that current patent law would provide sufficient incentive for new-use innovation if only pharmaceutical companies had sufficient information (about prescribing and dispensing) to enforce their patents.¹⁶⁴ In his model, therefore, a pharmacist would dispense the generic drug for the unapproved use and report the sale to the pharmacy benefit manager and innovator, allowing the innovator to bill the insurer directly for the sale.¹⁶⁵ If the new use was protected by patent, the invoice would presumably be presented as an alternative to suit for inducing patent infringement.

For this proposal to work for patents, the pharmacist would need to know how the patient planned to use the drug, and she would need to be required (or motivated) to report either all sales or all off-label sales to the payer and the innovator. This, too, could be tucked into the misbranding provisions. Rather than deeming it an act of misbranding to dispense a generic drug for a use that was carved out due to patent or exclusivity, Congress could deem it an act of misbranding to dispense a generic drug or biosimilar without disclosing the sale and diagnosis to the payer and the innovator—or perhaps to the government for inclusion in a database that aggregated data for innovators.¹⁶⁶ Again, however, the pharmacist would need to know the

¹⁶³ See *id.* at 36.

¹⁶⁴ See *id.* at 35–37, 51, 55.

¹⁶⁵ See *id.* at 59. In the alternative, the pharmacist could dispense the innovator's drug. See *id.*

¹⁶⁶ Professor Roin suggests a different statutory approach; he would have Congress allow drug companies “to require indication reporting whenever physicians prescribe [the] drug.” *Id.* at 61 n.431. He draws an analogy to use and distribution restrictions for high risk drugs under section 505-1 of the FDCA, pursuant to which a pharmacist or physician may be required to confirm the diagnosis of a patient before dispensing or administering a drug. See *id.* Professor Halabi responds that giving pharmaceutical companies access to information about prescribing practices “will generate as much or more off-label promotion activity and compromise the physician–patient relationship.” Halabi, *supra* note 36, at 70–73 (capitalization altered). Putting aside possible replies to Professor Halabi's speculation about generating off-label

patient's diagnosis, and perhaps this would be solved privately once the pharmacies faced liability for misbranding. But regulating communications between pharmacists and payers goes well beyond the current scope of FDA's authority. As a purely philosophical matter, this might be better in a stand-alone piece of legislation rather than the misbranding provisions of the drug statute.

It is possible this approach would end infringing sales rather than resulting in regular payments to innovators for those sales. The threat of suits for patent infringement, and the reality of paying for patent infringement, might prompt payers to construct systems that prevent dispensing for protected uses.¹⁶⁷

But this idea has several shortcomings. To begin with, it does nothing to address new uses protected by three-year exclusivity or orphan exclusivity, even though some new uses may be protected only by exclusivity. Exclusivity operates against FDA alone; there is no liability for infringing sales, nor is there any theory of induced liability. Without a credible threat of suit, an invoice from the innovator might be disregarded. Congress could enact liability for infringement of exclusivities, but doing so would be inconsistent with nearly a century of food and drug law. As a general rule, there are no private rights of action under the FDCA.¹⁶⁸

Even if we accepted a solution limited to new uses with patent protection, the proposed misbranding provision would work only because it creates the means for an enforcement-backed invoice to the payer. But it is not clear whether payers would view the threat of a patent infringement suit as credible. Payers are not appealing defendants for an innovator; they are the company's customers.

For this reason, some will argue that Congress should dispense with helping innovators enforce their patents and simply require payers to make innovators whole. Lost profits might be straightforward to calculate if the innovator had sold its product for the protected use before FDA approved the generic drug.¹⁶⁹ Presumably, this would end infringing sales by motivating

promotion, there is no obvious reason why a proposal that insurers compensate innovators for infringing sales requires innovators to receive patient-specific or physician-specific information.

¹⁶⁷ As Professor Roin points out, this could be accomplished by extending prior authorization systems to include new uses for approved drugs. *See* Roin, *supra* note 7, at 62–65.

¹⁶⁸ *See* 21 U.S.C. § 337(a) (2012) (“Except as provided in subsection (b) of this section, all such proceedings for the enforcement, or to restrain violations, of this chapter shall be by and in the name of the United States.”); *id.* § 337(b) (authorizing the states to restrain violations of certain food law provisions). *But see id.* § 399d(b)(7) (authorizing private suit by whistleblower in a food facility to require employer's compliance with an order providing relief to whistleblower).

¹⁶⁹ Lost profits are the default measure for compensatory damages for patent infringement. *Rite-Hite Corp. v. Kelley Co.*, 56 F.3d 1538, 1545 (Fed. Cir. 1995) (en banc), cert. denied 516 U.S. 867 (1995) (“[T]he general rule for determining actual damages to a patentee that is itself producing the patented item is to determine the sales and profits lost to the patentee because of the infringement.”). At a minimum the patentee is entitled to a reasonable royalty. 35 U.S.C. § 284 (2012).

payers to adopt whatever systems were necessary to avoid damages liability.¹⁷⁰ But there are reasons to object to this philosophically. Conceding infringing sales and working out a system for payment to the innovator renders the actual incentives—the patent and the exclusivity—effectively irrelevant. As for exclusivity, it means next to nothing for FDA approval to be withheld if federal law is arranged to condone sales despite the lack of approval and, indeed, creates a mechanism for compensation. In the case of patents, with a method for compensation that implicitly blesses infringement, it would be hard to claim that the patent still grants the right to exclude.

3. Generic Companies

Third, Congress could instead require payment by the generic companies whose drugs are sold and used for infringing purposes. As noted earlier, under current law there is very little prospect of private relief against the generic companies. Patent doctrine generally does not lead to generic liability for induced infringement, at least in the conventional pre-launch situation, and exclusivity cannot be privately enforced. But Congress could require a generic or biosimilar company to make the innovator whole for any sale lost because its product was dispensed for a use protected by patent or exclusivity. This legislation would be more complex than a narrow misbranding provision targeted at pharmacists, and it is subject to the same basic philosophical objection as legislation requiring payers to make innovators whole. An elaborate scheme for payment from generic companies to innovators, grounded in indication-specific pricing, amounts to giving up on new-use patents and exclusivity. There would be no right to exclude on the patent, as a practical matter.¹⁷¹ And the lack of regulatory approval for the uses in question would be a sham. This would be an attractive and simple solution, but it does violence to patent law and drug approval law.

If Congress took this approach, however, a generic drug manufacturer would need to track the extent to which the product was dispensed for unlabeled protected uses. This would require the cooperation of pharmacists and payers, which could be accomplished by making the payer jointly liable for each sale. Or, as an alternative to requiring payment tied to actual sales for infringing use, Congress could require the generic company and payer to make payments based on the percentage of sales expected to result from the unlabeled indication. For instance, if 85% of the innovator's sales (prior to

¹⁷⁰ Rebecca Eisenberg, Professor, University of Michigan, Panel Discussion at Session 2G of the University College London and Georgetown University Law Center's Clinical Innovation Conference, at 15 (Feb. 8–9, 2018) (transcript available at https://www.ucl.ac.uk/laws/sites/laws/files/ucl_georgetown_clinical-innovation-conference_transcript_09feb18_pm.pdf) [hereinafter SECOND MEDICAL USE CONFERENCE].

¹⁷¹ Consider, by way of analogy, the compulsory licensing provisions of copyright law. *E.g.*, 17 U.S.C. § 111(c)–(d) (2012) (granting cable companies a “statutory license” to retransmit a performance of a work embodied in a primary transmission by a broadcast station).

generic entry) were for the second-approved indication still under patent, then it stands to reason that—with automatic substitution—85% of the generic drug sales would be for the same indication. Or, if 85% of the prescriptions for the innovative product were written for the protected use, then presumably 85% of the generic drugs dispensed would be sold for the use in question. The obligation to make the innovator whole could be rebuttable with proof of the actual purpose of every sale. This would provide generic companies and payers with a strong incentive to develop systems for tracking the purpose of sales.

In the end, this too might stem the tide of infringing sales, rather than compensating the innovator for those sales. Unless the price of generic drugs increased to cover the payments for infringing sales, payments for infringing sales could be prohibitively high, which could prompt a private solution that prevented the infringing sales.¹⁷²

CONCLUSION

The legislative proposals described in Part IV reflect the intuition that multiple stakeholders are involved and responsible, when an infringing sale and use occur, and that these stakeholders could solve the new-use problem by working together. The proposals all take the same basic approach: create a credible threat of liability for one (or several) of these stakeholders to encourage them to work together to design that solution.

In theory, any of the three legislative approaches described in Part IV is actionable. And each has advantages and disadvantages. Placing the burden on the pharmacist makes some sense, for instance, because the pharmacist knows which generic drug the patient might receive and because the pharmacist is the last person in a position to prevent or conduct a sale for an infringing use. Placing the burden on the payer may make the most sense because payers play an intermediary role connecting the other stakeholders, they are well-positioned to require disclosure of the planned use from the physician, and they have the leverage to dictate to the pharmacy which product will be dispensed. But if this legislative strategy used the threat of a patent infringement case to motivate payers, it would leave out new uses that are protected only by new-use or orphan exclusivity. All three suggestions in Part IV would benefit from more vetting than possible in this Article, but placing the burden on the generic company by requiring lost-profit payment for the percentage of sales expected to result from unlabeled and protected indications would cover new uses protected by both patent and exclusivity, and it has the benefit of administrative simplicity. Imposing joint liability on payers would involve the party in the best position to bring everyone to the table quickly.

¹⁷² E.g., Brian Hirsch, Vice President, Global IP and Legal Head North America, Glenmark Pharmaceuticals, SECOND MEDICAL USE CONFERENCE, *supra* note 170, at 12.

There might be other ways to motivate payers, pharmacists, and generic drug companies to design a system that will prevent infringing sales and uses. The purpose of this Article is to point out that these stakeholders *could* solve the problem of new uses, if properly motivated, not to advocate for a particular way of motivating them.

The preceding discussion assumes both that new-use innovation will remain risky and expensive and that we want to continue to encourage this innovation with new-use patents and regulatory exclusivity. There are other ideas in the literature. Broadly speaking, we might change the drug regulatory paradigm or change the statutory incentives.

Changing the regulatory paradigm might mean reducing the burden of new-use research in the first place.¹⁷³ FDA is taking steps in this direction. Congress amended the FDCA in December, 2016, to require the agency to develop a framework for evaluating “real world evidence” to help support new-use approvals.¹⁷⁴ Although the new-use framework remains under development, the agency has used real world evidence to support decisionmaking in the past, and it expanded a drug’s indication on the basis of real world evidence in May, 2017.¹⁷⁵ One possibility might be to approve a new use on the basis of a smaller safety and effectiveness study plus real world evidence, subject to an obligation to conduct additional studies after approval of the use.¹⁷⁶ Whether this would reduce the overall cost of developing a new use

¹⁷³ An even more radical approach would be to shift to using public funds for new-use research and development. Cf. Jerome H. Reichman, *Rethinking the Role of Clinical Trial Data in International Intellectual Property Law: The Case for a Public Goods Approach*, 13 MARQ. INTELL. PROP. L. REV. 1, 51 (2009) (proposing that new drug development be publicly funded); Arti Rai, *Use Patents, Carve-Outs, and Incentives: A New Battle in the Drug Patent Wars*, 367 NEW ENG. J. MED. 491, 492 (2012) (suggesting that the “investment in well-designed trials” to show effectiveness of new uses “need not emerge . . . only from individual firms operating in secrecy and motivated by patents” and that “the public sector’s role is likely to increase”).

¹⁷⁴ 21st Century Cures Act, Pub. L. No. 114-255, 130 Stat. 1033 (codified as amended at 21 U.S.C. § 355g (Supp. 2017)). “Real world evidence” means data on usage, benefits, or risks that derive from sources other than traditional clinical trials. 21 U.S.C. § 355g(b). FDA officials have recently authored several scientific articles on the use of real-world evidence relating to medical products. See, e.g., Rachel E. Sherman et al., *Accelerating Development of Scientific Evidence for Medical Products Within the Existing US Regulatory Framework*, 16 NAT. REV. DRUG DISCOVERY 297 (2017); Rachel E. Sherman et al., *Real-World Evidence: What Is It and What Can It Tell Us?*, 375 NEW ENG. J. MED. 2293 (2016). The Agency has also developed thinking on the use of real-world evidence relating to medical devices. FDA, *USE OF REAL-WORLD EVIDENCE TO SUPPORT REGULATORY DECISION-MAKING FOR MEDICAL DEVICES* 4 (2017).

¹⁷⁵ FDA approved an extension of Kalydeco (ivacaftor)’s indication from 10 cystic fibrosis mutations to 33 mutations, based on registry data and laboratory research. Cole Werble, *Real-World Evidence: Advice, Principles and Examples Emerge from FDA*, PINK SHEET (Oct. 7, 2017, 4:22 PM), <https://pink.pharmaintelligence.informa.com/PS121715/RcalWorld-Evidence-Advice-Principles-And-Examples-Emerge-From-FDA>.

¹⁷⁶ This would be consistent with a broader trend in the regulation of new drugs, recently described by Professor Price as a “gradually shifting toward a blended approach—a ‘life-cycle’ approach to developing evidence, in the words of an influential Institute of Medicine report—where information gathering

remains to be seen, though it has the potential to speed its approval.¹⁷⁷ If it resulted in new-use approval earlier in a drug's lifecycle, the additional time to market the new use under the compound exclusivity and patent might be valuable and partially mitigate the lack of meaningful protection for the new use itself. After the compound exclusivity and patent expired, however, the reduced premarket burden for new-use approval might be insufficient to motivate new-use innovation. The innovator would still need a way to recover the investment and pay for any post-approval confirmatory trials, and automatic substitution would defeat its exclusivity.

Rather than reducing the regulatory burden of new-use approval, Congress might instead increase the incentive for new-use research.¹⁷⁸ Simply increasing the length of new-use exclusivity, however, does not address the basic problem described in this Article. The new use must also be excludable. For this reason, some suggest increasing the basic data exclusivity term.¹⁷⁹ At the very least, data exclusivity for new chemical entities could be increased to the twelve years that biologics enjoy.¹⁸⁰ The basic compound exclusivity prevents approval of a generic or biosimilar for any use for a period of time. Lengthening the compound exclusivity for new drugs to twelve years would provide an incentive for companies to develop new uses of those drugs for at least a decade after initial FDA approval. This is because the new use would be effectively excludable during the balance of the compound exclusivity term. Further lengthening the term of the compound exclusivity for drugs and biologics—for example, to fifteen or seventeen years—would have the same effect, and there has been some legislative interest in allowing innovators to

both before and after approval are each key to regulation of drugs.” W. Nicholson Price II, *Drug Approval in a Learning Health System*, 102 MINN. J. 2413, 2430–31 (2018).

¹⁷⁷ Use of real-world evidence might not reduce the overall risk or cost, if the innovator was required to confirm safety and effectiveness for the new use after approval and if policymakers remained committed to the substantial evidence standard for effectiveness.

¹⁷⁸ Professor Roin has suggested, for instance, that three years is insufficient to motivate investment in new uses that require extensive trials. Roin, *supra* note 7, at 71.

¹⁷⁹ Consider, for instance, the proposal from Robert Armitage, former General Counsel of Eli Lilly, that policymakers enact legislation offering drug innovators the option to elect a fixed period of protection from generic competition, in exchange for expiry of key patents (such as those protecting the drug's active ingredient, physical form, formulation, and uses) fourteen years after approval. Robert A. Armitage, IP Strategy & Policy Consultant, Marco Island, Panel Discussion at Session 2C of the University College London and Georgetown University Law Center's Clinical Innovation Conference, at 15 (Feb. 9, 2018) (transcript available at https://www.ucl.ac.uk/laws/sites/laws/files/ucl_georgetown_clinical-innovation-conference_transcript_09feb18_am.pdf).

¹⁸⁰ See Ryan Timmis, *The Biologics Price Competition and Innovation Act: Potential Problems in the Biologic-Drug Regulatory Scheme*, 13 NW. J. TECH. & INTELL. PROP. 215, 223 (2015). Under current law, a generic application cannot be submitted until five years after new chemical entity exclusivity, although this period drops to four years if the generic applicant challenges a patent. 21 U.S.C. § 355(j)(5)(F)(ii) (2012). If the patent owner brings a timely suit, FDA cannot approve the generic application for another 30 months or until 7.5 years after new chemical entity approval, whichever comes later. *Id.*; *id.* § 355(j)(5)(B)(iii).

opt into longer exclusivity by disclaiming patent coverage.¹⁸¹ Indication-based pricing might be a way for the innovator to recover the new-use investment in the later years without an unexpected and unwelcome increase in the price for established uses. But legislation that simply modified the data exclusivity term would not in itself provide any incentive for payers and pharmacists to adopt systems that tracked prescribing and dispensing by planned use.

Tackling the new-use problem through longer exclusivity for the compound is appealing because many factors contributing to the problem (the scope of AB ratings, the content and layout of Orange Book, state substitution laws, and pharmacy and payer practices) are entrenched in our healthcare system. But longer exclusivity on the compound could be controversial. Some would find it an over-inclusive solution on the theory that it would delay generic and biosimilar versions of the molecule past expiry on the composition of matter patent simply to encourage new-use innovation that might or might not happen. An alternative, responding to this concern, might adopt a variation of the European approach to new-use exclusivity, allowing extension of the compound exclusivity if the innovator secured approval of significant new uses, not to exceed some total number of years, such as twelve or fifteen.¹⁸² But even this solution is imperfect. Towards the end of the exclusivity period, the value of the incentive would drop (unless the innovator could adopt indication-based pricing), which might affect which types of new uses were pursued. Moreover, the solution would do nothing for new-use innovation after the core exclusivity on the compound expired.

The problem with increasing the incentive for new-use research is that there is nothing wrong with the current incentives. Putting aside potential uncertainty about new-use patents injected by the Supreme Court's recent patent eligibility rulings,¹⁸³ patents and regulatory exclusivity are adequate for the task of encouraging new-use innovation. The theory of incentivizing through excludability is solid. We have simply allowed new-use excludability to be gutted by a combination of imprecise and overbroad agency, payer, prescriber, and pharmacy practices and policies. In principle, the solution should be to modify those practices and policies so new-use patents and regulatory exclusivity work as Congress intended.

¹⁸¹ See e.g., MODDERN Cures Act of 2011, H.R. 3497, 112th Cong. § 2 (2011); MODDERN Cures Act of 2013, H.R. 3116, 113th Cong. § 103 (2013). These bills generally track Mr. Armitage's proposal. See Armitage, *supra* note 179, at 15.

¹⁸² In addition to providing one year of exclusivity for a new use supported by significant preclinical or clinical data, no matter when that use is approved, European law provides an extra year of exclusivity on the compound for a new indication approved in the first eight years that "bring[s] a significant clinical benefit in comparison with existing therapies." Krista Carver, Jeffrey Elikan, & Erika Lietzan, *An Unofficial Legislative History of the Biologics Price Competition and Innovation Act of 2009*, 65 FOOD & DRUG L. J. 671, 691 (2010).

¹⁸³ See *supra* note 57.

Recasting the problem this way—as the gutting of extant federal law—avoids one of the challenges faced by scholars of innovation policy: the challenge of assessing the but-for world. Scholarship that points to shortcomings in domestic innovation policy suffers from an intrinsic proof problem; it is hard to prove what might have been developed and approved had the rules in the past been different. Often, we respond by explaining the potential for harm to the public health. Exclusivity provides an incentive to study new uses. In the absence of exclusivity, the research will not be done, which means that important new uses will remain unexplored. So, we offer examples of uses that *should* be explored. Professor Roin’s unpublished paper contains a rich discussion of lost medical treatments.¹⁸⁴ Professor Halabi has offered a detailed case study of metformin, which is approved for treatment of diabetes but thought to have potential to treat nonalcoholic fatty liver disease, polycystic ovary syndrome, Alzheimer’s disease, obesity, and cancer.¹⁸⁵ He points to a “narrative now prevailing in the scholarly literature,” that the companies responsible for metformin have not explored these alternatives “because there is no incentive to do so.”¹⁸⁶ And the literature is full of examples of approved drugs that might have promise in other diseases.¹⁸⁷

We do not have sufficient information to know whether, and to what extent, the lack of new-use excludability has deterred companies that might otherwise have invested in the research. Nor do we know that making new uses excludable will solve the problem. To some extent, this Article avoids the problem of proof, because it does not propose a *change* in federal innovation policy. It casts the problem as the fact that existing incentives—patents and exclusivity already enacted by Congress and applicable to new uses—are undermined. Congress meant for new uses to be excludable, and currently they are not.

In light of some of the more radical proposals on the table, that range from publicly funding all new drug research to lengthening data exclusivity for all new medicines, taking steps to ensure that new use patents and exclusivity simply operate as intended would be a reasonable and moderate first

¹⁸⁴ Roin, *supra* note 7, at 40–45.

¹⁸⁵ See generally Halabi, *supra* note 36.

¹⁸⁶ *Id.* at 45.

¹⁸⁷ Hundreds of scientific articles discussing the repurposing of drugs appear in the National Library of Medicine database. *E.g.*, Shuchi Mittal, *β-Adrenoreceptor Is a Regulator of the α-synuclein Gene Driving Risk of Parkinson’s Disease*, 357 *SCIENCE* 891, 891 (2017) (suggesting that clenbuterol—an asthma medication approved in other countries—may have promise for treatment of Parkinson’s); Theodore Keats et al., *The Rationale for Repurposing Sildenafil for Lung Cancer Treatment*, 18 *ANTI-CANCER AGENTS MED. CHEMISTRY* 367, 367 (2017) (noting “a considerable body of evidence” that sildenafil—the active ingredient in Viagra, indicated to treat erectile dysfunction—has “anticancer properties”); Bernhard W. Renz et al., *Repurposing Established Compounds to Target Pancreatic Cancer Stem Cells (CSCs)*, 5 *MED. SCI.* 14, 14–15 (2017) (suggesting a variety of compounds to target a variety of cancer types based on emerging evidence such as the antiemetic agent aprepitant for pediatric liver cancer).

step. A narrow fix that makes these incentives work as they were indisputably intended should not require new normative or empirical justification.¹⁸⁸

One problem policymakers would face, though, is that the current approach to drug prescribing, dispensing, coverage, and reimbursement may be entrenched. The question is whether the benefits of inertia justify missing out on significant new cures. Policymakers focus more on drug prices today than they do on innovation policy. But meaningful innovation incentives are an investment in the future. The question is if we do not act today to repair the existing incentives for new-use innovation, we will regret our inaction in the future—when it is too late.

¹⁸⁸ Additional normative and empirical work could, however, be helpful. For instance, it may help to understand why — given the problem described in this Article — companies develop any new uses at all. It is possible that most new uses are introduced before the compound exclusivity and patent expire, and that the others necessitate a change in the product (such as a new route of administration) that is itself protected. The author is generating a dataset that will permit some empirical examination of this question.