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Research Fellow, Petrie-Flom Center for Health Law Policy, Biotechnology, and Bioethics, Harvard Law School. I wrote this Article during my time as a Visiting Associate Professor & Frank H. Marks Intellectual Property Fellow at George Washington University Law School and as a Fellow at the Hanken School of Economics. I gratefully acknowledge the financial support from the Academy of Finland research project, Fairness, Morality and Equality in International and European Intellectual Property Law (FAME-IP). For comments and suggestions, I thank Michael Abramowicz, Amy Kapczynski, Edith Beerdsen, Sam Brunson, Dan Burk, Rebecca Eisenberg, Scott Kieff, Lynn LoPucki, Lidiya Mishchenko, Faraz Sanei, Sonia Suter, James Tierney, the participants at the 2020 Intellectual Property Scholars Conference at Stanford Law School, the Junior Scholars Workshop, the Seminar on IPR and Pharmaceutical Innovation at the Hanken School of Economics, the 18th Annual Works-in-Progress in Intellectual Property Colloquium hosted by American University Washington College of Law, Texas A&M University School of Law, and University of Utah S.J. Quinney College of Law, the American Association of Law School's New Voices in IP Program, and the Third IP & Innovation Researchers of Asia (IPIRA) Conference. I owe special thanks to Dhanay Cadillo Chandler, Samuel F. Ernst, Dmitry Karshtedt, Erika Lietzan, Lisa Larrimore Ouellette, W. Nicholson Price II, Rachel Sachs, and Ana Santos Rutschman, all of whom provided extensive feedback. I thank the Georgia Law Review for the diligent work.

OFF-LABEL INNOVATION

David A. Simon[*]

Modern medicine faces many significant problems. This Article is about two of them. The first is that approved drugs have many potential therapeutic uses that are never identified, investigated, or developed. The second is the routine practice of physicians prescribing approved drugs for unapproved uses—so-called "off-label" uses. These problems seem very different. Failure to invest in potential new uses is an innovation problem: firms lack incentives to research and develop new uses of old drugs. The problem of off-label uses, on the other hand, is one of safety and efficacy: off-label uses are risky because they are not supported by the same level of evidence as approved uses. While descriptively accurate, this is not the only accurate description. Each of these problems is also one of information—a lack of information about the safety and efficacy of prescribing approved drugs for unapproved uses. Because all new uses of approved drugs are off-label uses, gathering safety and efficacy information about off-label uses, in effect, produces safety and efficacy information about many new uses. Not only

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that, but some off-label uses may be new: physicians may innovate by prescribing drugs off-label. Reframing these two seemingly disparate problems in terms of a common information deficit enables a single, information-based solution. This solution—which draws on the existing suite of innovation policy levers—incentivizes providers, rather than pharmaceutical companies, to generate the post-market information needed to address both problems.

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I. INTRODUCTION

In 1966, the Food and Drug Administration (FDA) approved the drug amantadine hydrochloride (amantadine) for the prevention of Asian influenza A (H2N2).[1] Doctors began prescribing the drug shortly thereafter.[2] One patient who was prescribed the drug also happened to suffer from Parkinson's disease (Parkinson's).[3] To her surprise—and the surprise of her neurologists—many of her neurological symptoms lessened shortly after starting a course of the medication.[4] Those doctors—who noted that "[s]uch serendipitous findings are not rare[,] . . . especially in chronic diseases"—proceeded to study amantadine's effect on Parkinson's.[5] But it would be another seven years before the FDA approved amantadine to treat that condition.[6]

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[1] Thomas H. Maugh II, *Panel Urges Wide Use of Antiviral Drug*, 206 SCIENCE 1058, 1058 (1979) (noting FDA approval following clinical trials that demonstrated 70 percent reductions in illness from influenza A).

[2] The story of amantadine's unanticipated development is recounted in G. Hubsher, M. Haider & M.S. Okun, *Amantadine: The Journey from Fighting Flu to Treating Parkinson Disease*, 78 NEUROLOGY 1096, 1096–99 (2012).

[3] *See id.* ("[A] 58-year-old woman with [Parkinson's] had reported . . . an improvement in rigidity, tremor, and akinesia while taking amantadine for flu.").

[4] Robert S. Schwab, Albert C. England, Jr., David C. Poskanzer & Robert R. Young, *Amantadine in the Treatment of Parkinson's Disease*, 208 JAMA 1168, 1168 (1969) ("[S]he experienced a remarkable remission in her symptoms of rigidity, tremor, and akinesia.").

[5] *Id.*; *see also* Robert S. Schwab, David C. Poskanzer, Albert C. England, Jr., & Robert R. Young, *Amantadine in Parkinson's Disease: Review of More Than Two Years' Experience*, 222 JAMA 792, 792–95 (1972) (describing prospective observational research).

[6] *See* Letter from Henry E. Simmons, Director, U.S. Food & Drug Admin., to E.I. du Pont de Nemours & Co. (Apr. 17, 1973) (on file with author) [hereinafter U.S. Food & Drug Admin., Notice of Approval] (approving Amantedine); Maugh, *supra* note 1, at 1058 (noting that the FDA approved Symmetrel, DuPont's trade name for amantadine, to treat Parkinson's in 1973*); see also* J. Máté et al., *Prophylactic Use of Amantadine During Hong Kong Influenza Epidemic*, 17 ACTA MICROBIOLOGICA ACADEMIAE SCIENTAIARUM HUNGARICAE 285, 285 (1970) (evaluating prophylaxis of drug for "Hong Kong flu"); U. Strömberg, T.H. Svensson & B. Waldeck, *On the Mode of Action of Amantadine*, 22 J. PHARMACY & PHARMACOLOGY 959, 961 (1970) (observing that the drug's effectiveness against Parkinson's is "brought about by an amphetamine-like mechanism"); Stanley Fahn, George Craddock & Gerald Kumin, *Acute Toxic Psychosis from Suicidal Overdosage of Amantadine*, 25 ARCHIVES NEUROLOGY 45, 45 (1971) (hypothesizing that amantadine functions similarly to other Parkinson's drug treatments by releasing dopamine from neuronal storage sites); B. Cox & C.S. Williams, *Cardiovascular Responses to Amantadine Hydrochloride in the Rat and Rabbit*, 43 BRITISH

In the interim, and even after its approval for Parkinson's,[7] doctors would prescribe amantadine for an increasing number of unapproved conditions, including shingles,[8] chronic fatigue syndrome,[9] hepatitis,[10] autism,[11] Jakob-Creutzfeldt Disease,[12]

J. PHARMACOLOGY 575P, 575P (1972) (investigating the cardiovascular actions of amantadine).

[7] Amantadine has undergone several labeling changes relating to Parkinson's, and the FDA has approved new forms of the drug as recently as 2018. *See Amantadine*, PARKINSON'S FOUNDATION, https://www.parkinson.org/Understanding-Parkinsons/Treatment/Prescription-Medications/Amantadine-Symmetrel (last visited Mar. 2, 2022) (listing different forms of amantadine used to mitigate Parkinson's).

[8] *See, e.g.*, A.W. Galbraith, *Treatment of Acute Herpes Zoster with Amantadine Hydrochloride (Symmetrel)*, 4 BRIT. MED. J. 693, 693 (1973) (stating that the study of 100 patients was initiated after the author received personal communication from another physician, G.H. Lloyd, who reported that "amantadine reduced the duration of pain, produced more rapid healing, and prevented postherpetic neuralgia").

[9] *See* Marjorie A. Bowman, Julienne K. Kirk, Robert Michielutte & John S. Preisser, *Use of Amantadine for Chronic Fatigue Syndrome*, 157 ARCHIVES INTERNAL MED. 1264, 1264 (1997) (explaining that a four-patient trial was stimulated by other research showing use of amantadine and symptom reduction (fatigue) in patients suffering from multiple sclerosis).

[10] *See* Jill Palmer Smith, *Treatment of Chronic Hepatitis C with Amantadine*, 42 DIGESTIVE DISEASES & SCIS. 1681, 1682 (1997) (stating that the purpose of study was to test the "safety and efficacy of amantadine in patients with chronic hepatitis C infection"); Isabelle Fouchard Hubert, Françoise Lunel, Jean-François Cadranel, Frédéric Iberti & Paul Calès, *Treatment of Chronic Hepatitis C with Amantadine*, 94 AM. J. GASTROENTEROLOGY 2316, 2316–17 (1999) (reporting an open-label, prospective pilot study of sixteen patients based on Smith's initial report and finding that amantadine was not effective in inducing a biochemical or virological response in patients suffering from chronic hepatitis C); Pierre Deltenre et al., *Evaluation of Amantadine in Chronic Hepatitis C: A Meta-Analysis*, 41 J. HEPATOLOGY 462, 462–73 (2004) (finding mixed results and suggesting further clinical trials on amantadine for chronic hepatitis C).

[11] *See* Bryan H. King et al., *Double-Blind, Placebo-Controlled Study of Amantadine Hydrochloride in the Treatment of Children with Autistic Disorder*, 40 J. AM. ACAD. CHILD & ADOLESCENT PSYCHIATRY 658, 659 (2001) (hypothesizing amantadine might be effective in treating neurobehavioral disorders based on its mechanism of action and limited reports in the medical literature, including as treatment for brain injury).

[12] For example, one doctor published an article explaining how he treated a patient with Jakob-Creutzfeldt Disease, a rare neurodegenerative disease affecting the brain. *See* J. Braham, *Jakob-Creutzfeldt Disease: Treatment by Amantadine*, 4 BRIT. MED. J.212, 213 (1971) (noting that the doctor hypothesized that amantadine might be effective based on its initial results treating Parkinson's disease).

epilepsy,[13] and traumatic brain injury (TBI).[14] And they would do so despite the unknown efficacy and risks of prescribing amantadine

[13] *See* W. Donald Shields, Jean L. Lake & Harry T. Chugani, *Amantadine in the Treatment of Refractory Epilepsy in Childhood: An Open Trial in 10 Patients*, 35 NEUROLOGY 579, 579 (1985) (noting that the authors first administered the drug to two patients based on a hypothesized link to amantadine's mechanism of action and noticed immediate reduction in symptoms and then proceeded to conduct a ten-patient open trial (citing L.F. Quesney, F. Andermann & P. Gloor, *Dopaminergic Mechanism in Generalized Photosensitive Epilepsy*, 31 NEUROLOGY 1542, 1542–44 (1981))). This, in turn, has spurred further investigation into amantadine's use in other epileptic conditions. *See* Rujuta B. Wilson, Yazan Eliyan, Raman Sankar & Shaun A. Hussain, *Amantadine: A New Treatment for Refractory Electrical Status Epilepticus in Sleep*, 84 EPILEPSY & BEHAV. 74, 75 (2018) (testing the hypothesis that "amantadine may target mechanisms that underlie ESES and associated epileptic encephalopathy").

[14] In 1988, one doctor posited that amantadine might be helpful to treat brain injuries based on anecdotal reports "suggest[ing] that amantadine may have some benefit in the chronic TBI patient," as well as limited research on rats. C. T. Gualtieri, *Pharmacotherapy and the Neurobehavioural Sequelae of Traumatic Brian Injury*, 2 BRAIN INJURY 101, 107 (1988) (discussing Rocco F. Marotta, Nancy Logan, Michael Potegal, Murray Glusman & Eliot L. Gardner, *Dopamine Agonists Induce Recovery from Surgically-Induced Septal Rage*, 269 NATURE 513, 513 (1977)); *see also* Thomas Gualtieri, Mark Chandler, Tena B. Coons & Lloyd T. Brown, *Amantadine: A New Clinical Profile for Traumatic Brain Injury*, 12 CLINICAL NEUROPHARMACOLOGY 258, 260 (1989) (discussing the author's previous innovative off-label use as the impetus for undertaking study of amantadine for brain injury (citing Mark C. Chandler, Jarrett L. Barnhill & C. Thomas Gualtieri, *Amantadine for the Agitated Head-Injury Patient*, 2 BRAIN INJURY 309, 310 (1988))); Gualtieri et al., *supra*, at 260 (discussing how amantadine could be used to treat patients with head injuries). That hypothesis was subsequently taken up in limited research. *See, e.g.*, Marilyn F. Kraus & Pauline M. Maki, *Effect of Amantadine Hydrochloride on Symptoms of Frontal Lobe Dysfunction in Brain Injury: Case Studies and Review*, 9 J. NEUROPSYCHIATRY CLINICAL NEUROSCIENCES 222, 224 (1997) (reviewing the literature and noting that amantadine's "use in other disorders, such as epilepsy, dementia, and brain injury, has been prompted by case studies or small controlled studies showing improvements in cognitive functioning, EEG records, activity levels, or depressive symptoms"); R. Van Reekum et al., *N of 1 Study: Amantadine for the Amotivational Syndrome in a Patient with Traumatic Brain Injury*, 9 BRAIN INJURY 49, 50 (1995) (stating that the hypothesis of the study was that amantadine would improve the rehabilitation of a patient with amotivational syndrome, which developed after a traumatic brain injury). It is also interesting to note that one of these physicians continued to find innovative off-label use of another drug, methylphenidate (Ritalin), for the same condition (TBI). *See* Randall W. Evans, C Thomas Gualtieri & Debra Patterson, *Treatment of Chronic Closed Head Injury with Psychostimulant Drugs: A Controlled Case Study and an Appropriate Evaluation Procedure*, 175 J. NERVOUS & MENTAL DISEASE 106, 109 (1987) (noting that closed head injury patients "may find partial relief from attentional, memory, and behavioral impairments" after taking methylphenidate). Methylphenidate is now commonly used to treat the sequelae of TBI. *See* Samir Al-Adawi et al., *Methylphenidate Improves Executive Functions in Patients with Traumatic Brain Injuries: A Feasibility Trial*

for new indications in populations—some of whom probably took other medications—with underlying health conditions. Researchers identified some of these potential uses from the initial investigation spurred by the first patient report.[15] Other uses, including amantadine's uses for treating Jakob-Creutzfeldt Disease and epilepsy, were tested by physicians prescribing this approved drug for unapproved uses—they were prescribing "off-label."[16]

How were so many doctors prescribing approved drugs for such different unapproved uses, especially given that those unapproved uses had unknown risks? While this may seem puzzling, it is actually quite common. Physicians frequently prescribe drugs off-label.[17] And in some areas of medicine, such as cardiology and psychiatry, off-label prescriptions predominate.[18] Yet, the discovery of amantadine as a treatment for Parkinson's and other conditions, and its slow development for many of those uses, highlights two important problems for medicine that remain unsolved—and how to solve them.

One is the "Problem of Off-Label Uses."[19] Off-label uses may not be supported by the same level of evidence as approved, on-label uses. Patients prescribed drugs off-label are, therefore, subjected to a greater risk of harm. The risk, however, is often necessary for patients with limited or no efficacious on-label treatments. At the time doctors discovered that amantadine might have some effect on Parkinson's, for example, no known curative treatments for it

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via the Idiographic Approach, 20 BMC NEUROLOGY 103, 104 (2020), https://bmcneurol.biomedcentral.com/track/pdf/10.1186/s12883-020-01663-x.pdf.

[15] *See, e.g.*, Hubsher, *supra* note 1, at 1098 (noting that the initial research spurred the role of L-dopa as a response predictor).

[16] *See* David C. Radley, Stan N. Finkelstein & Randall S. Stafford, *Off-label Prescribing Among Office-Based Physicians*, 166 ARCHIVES INTERNAL MED. 1021, 1025 (2006) (explaining the background of off-label medicine use).

[17] *See id.* at 1025 (finding that "about 21% of all estimated uses for commonly prescribed medications were off-label").

[18] *See id.* at 1023–25 ("Off-label use was most common among cardiac Medications."); *see, e.g.*, CAVALLA, *infra* note 86, at 13 (noting the prevalence of off-label prescriptions "may be up to 90% in some hospitalised paediatric patients"),

[19] *See* Ryan Abbott & Ian Ayres, *Evidence and Extrapolation: Mechanisms for Regulating Off-Label Uses of Drugs and Devices*, 64 DUKE L.J. 377, 388 (2014) ("The central problem with off-label use is that there is an information deficit.").

existed.[20] Like all off-label uses, amantadine's safety and efficacy profile for Parkinson's was largely unknown because it hadn't been researched either through observational studies (where researchers make observations without any interventions)[21] or experimental randomized controlled clinical trials (RCT)[22] (where researchers typically randomize subjects into treatment and control groups and ensure that neither the subject nor the researcher knows who is in which group).[23] The same is true for its current off-label use by doctors to treat many other conditions, such as TBI.[24]

One reason for the lack of research into new uses of existing drugs, including widespread off-label uses, is because of a different challenge, dubbed the "Problem of New Uses"[25]: patent law and drug regulation—which work well for some kinds of novel drug development[26]—don't always provide sufficient economic incentives

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[20] Even today there is no known cure. Most therapies attempt to address the neuromotor symptoms that the disease causes. *See e.g.*, Hubsher, *supra* note 1, at 1097 (noting that several prior animal studies focused on symptoms of "psychomotor agitation").

[21] *See* ALLAN K. HACKSHAW, A CONCISE GUIDE TO OBSERVATIONAL STUDIES IN HEALTHCARE 1–24 (2015). Observational studies can take different forms. *Id.* at 10–13.

[22] *See, e.g.*, DAVID MACHIN & PETER M. FAYERS, RANDOMIZED CLINICAL TRIALS: DESIGN, PRACTICE AND REPORTING 23–39 (2010) (explaining the general structure of randomized clinical trials); SHEIN-CHUNG CHOW & JEN-PEI LIU, DESIGN AND ANALYSIS OF CLINICAL TRIALS: CONCEPTS AND METHODOLOGIES 167–207 (3d ed. 2014) (reviewing eight design types of clinical trials); TOM BRODY, CLINICAL TRIALS: STUDY DESIGN, ENDPOINTS AND BIOMARKERS, DRUG SAFETY, AND FDA AND ICH GUIDELINES 131–41 (2011) (describing one and two arm trials).

[23] Some aspects of the amantadine drug safety profile were known from previous applications. *See* Hubsher, *supra* note 1, at 1097. But the safety and efficacy profile for the specific dosages, indication, and patient populations was unknown. *See id.*

[24] *See supra* note 14 and accompanying text.

[25] *See* Rebecca S. Eisenberg, *The Problem of New Uses*, 5 YALE J. HEALTH POL'Y L. & ETHICS 717, 717 (2005) [hereinafter Eisenberg, *The Problem of New Uses*] (examining "the problem of motivating firms to invest in rigorous testing of new uses for previously approved drugs"); *see also* Benjamin N. Roin, Solving the Problem of New Uses 2–3 (Oct. 14, 2016) (unpublished manuscript), https://www.bu.edu/law/files/2016/10/Solving-the-Problem-of-New-Uses-Benn.-Roin.pdf ("This well-known gap in the incentives for pharmaceutical innovation—known as 'the problem of new uses'—causes most (and perhaps almost all) of these potential new medical treatments to remain untested hypotheses." (footnotes omitted)).

[26] *See infra* note 28 and accompanying text. *But see* Eric Budish, Benjamin N. Roin & Heidi Williams, *Do Firms Underinvest in Long-Term Research? Evidence from Cancer Clinical Trials*, 105 AM. ECON. REV. 2044, 2044–85 (2015) (noting that existing incentives can actually discourage investment in clinical trials with longer lag times from invention to commercialization and that existing patent laws reinforce this phenomenon by rewarding the

for companies to research and develop (R&D) new uses for old drugs (and existing off-label uses).[27] Although R&D for new uses is much cheaper than R&D for new drug molecules,[28] firms often don't pursue it because they can't exclude others (enough) from using the results.[29]

Research on amantadine illustrates this.[30] The FDA approved amantadine in 1966, the same year the United States Patent and Trademark Office (PTO) issued to DuPont two patents related to amantadine.[31] From 1966 until 1983 when amantadine's patents expired—and especially before Congress enacted the Hatch-

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inventor of a pharmaceutical with longer patent terms (via patent term extensions) and penalizing greater commercial lags with shorter patent terms).

[27] The general phenomenon of finding new uses for existing compounds is called "repurposing" or "repositioning." Sometimes this means only finding new uses of approved drugs; other times it means finding new uses of approved drugs or abandoned pharmaceutical candidates. *Compare* Marina Sirota et al., *Discovery and Preclinical Validation of Drug Indications Using Compendia of Public Gene Expression Data*, 3 SCI. TRANSLATIONAL MED. 96ra77, 96ra77 (2011) (using the former definition), *with* Divya Sardana et al., *Drug Repositioning for Orphan Diseases*, 12 BRIEFINGS IN BIOINFORMATICS 346, 346 (2011) (using the latter definition).

[28] There are almost no studies documenting the clinical development time for new indications of existing drugs. *But see, e.g.*, Joseph A. DiMasi, *Innovating by Developing New Uses of Already-Approved Drugs: Trends in the Marketing Approval of Supplemental Indications*, 35 CLINICAL THERAPEUTICS 808, 809, 816–17 (2013) [hereinafter DiMasi, *sNDAs*] (analyzing the "application-review times for new uses of already-approved drugs").

[29] *See* Amy Kapczynski & Talha Syed, *The Continuum of Excludability and the Limits of Patents*, 122 YALE L.J. 1900, 1942–43 (2013) (explaining that "there are some highly nonexcludable goods whose development a patent system will fail to incentivize because the private returns appropriable using patents remain lower than the private costs of creation or validation").

[30] Another example is chenodeoxycholic acid (Chenodiol), which physicians discovered as an off-label treatment for cerebrotendinous xanthomatosis (CTX) decades ago. *See* Dr. Patroula Smpokou, Remarks at Nat'l Ctr. for Advancing Translational Scis. Meeting: Repurposing Off-Patent Drugs: Research & Regulatory Challenges 63 (Apr. 6, 2020) [hereinafter NCATS Meeting], https://ncats.nih.gov/files/repurposing-off-patent-drugs_research--regulatory-challenges_day-1-transcript_04-06-2020.pdf. Since then, physicians have used the drug off-label as the treatment of choice for CTX, and it is now the standard of care. *Id.* No company has sought a Supplemental New Drug Application (sNDA) or New Drug Application (NDA) for Chenodiol to treat CTX.

[31] *Compare* U.S. Food & Drug Admin., Notice of Approval, *supra* note 6 (approving amantadine for use in treating Parkinson's), *with* U.S. Patent No. 3,391,142 (filed Feb. 9, 1966) (issued July 2, 1968).

Waxman Act in 1984[32]—DuPont had incentives to invest in clinical trials needed to obtain FDA approval for other possible indications, including Parkinson's.[33] The strength of these incentives, of course, waned as 1983 and 1984 drew closer, and largely dried up thereafter.[34] As the patent term decreased, DuPont's ability to recoup investment costs and turn a profit also decreased.[35] Because shrinking patent terms framed smaller and smaller windows to generate a return, incentives to invest in new uses of the patented drug decreased along with the patent term.

When the patent expired, generics could enter the market and drive down the price of the drug.[36] Research on new uses of amantadine, as a result, hasn't moved as quickly as research on its use to treat Parkinson's, for example.[37] This problem does not disappear *even if* pharmaceutical companies have the proper incentives to invest in research of some off-label or new uses. There are thousands, potentially tens of thousands, of new uses; it's impossible for drug companies to finance clinical trials for every new use, or even for a majority of them.

These two Problems seem separate and unrelated—and most scholars have approached them that way.[38] The Problem of Off-Label Uses is a safety and efficacy problem: off-label use is

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[32] *See* U.S. Patent No. 3,256,329 (filed June 9, 1964) (issued June 14, 1966) (issuing an original patent for amantadine); U.S. Patent No. 3,257,456 (filed May 4, 1964) (issued June 21, 1966) (issuing patent for "2-Adamantanone and derivatives"). Although the patents expired in 1983, the existing regulatory regime made it difficult for generics to enter the market even after a patent expired. *See infra* Section II.B. That changed with the Hatch-Waxman Act of 1984. *See infra* Section II.B. Given the limited evidence, it is not entirely clear whether it was the patent or the Hatch-Waxman Act that changed the investment landscape.

[33] See *infra* Section II.B.

[34] *See supra* note 32.

[35] *See infra* note 147.

[36] Generics did enter the market in 1987 when FDA approved Upsher Smith Labs' Abbreviated New Drug Application (ANDA). *See Product Details for ANDA 070589*, ANDA: 070589, U.S. FOOD & DRUG ADMIN., .https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=A&Appl_No=070589#23616, (last visited Mar. 5, 2022) (noting that Upsher Smith Laboratories LLC applied for the approval and that the drug was approved on August 5, 1986).

[37] There are a variety of other relevant differences between drug approval now and drug approval in 1973 that make the comparison inexact.

[38] I refer to the "Problem of New Uses" and the "Problem of Off-Label Uses" collectively as "the Problems." When I discuss either individually, I refer to them, where appropriate, as "Problem."

potentially harmful and wasteful because doctors prescribe drugs for unapproved uses without sufficient evidence of the safety and efficacy to support them. The Problem of New Uses is an innovation problem: pharmaceutical companies lack incentives to invest in R&D of new uses of approved drugs.[39] Framing the Problems separately leads many scholars to propose discrete solutions to each of them. Scholars focused on off-label use have, by and large, proposed limitations on the practice.[40] Those concerned with new uses, by contrast, recommend various tweaks to patent law and market exclusivity to capture new uses.[41] While the former attempt to reduce unnecessary off-label use, the latter try to increase the number of safe and effective new uses. Unfortunately, neither has succeeded—and it's still unclear how to make headway in either domain.

One reason the Problems seem intractable is because of the way they are framed—as separate and unrelated. This Article's first contribution is to make them tractable by reframing them in terms of their commonalities, rather than their differences: the information needed to solve, or at least ameliorate, both Problems is often the same information. Because all new uses of approved drugs are off-label uses, safety and efficacy information about approved new uses is also safety and efficacy information about off-label uses. Safety and efficacy information about off-label uses, in many cases, will also be safety and efficacy information about new uses. Put another way, information about off-label uses can be information about new uses, and information about new uses is always information about off-label uses.[42]

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[39] *See* Kapczynski & Syed, *supra* note 29 (explaining that patent law can have distortive (demand) effects because some kinds of informational goods can be difficult to exclude despite their high social value that cannot be resolved by resorting to internal features of patent law and arguing that government should be involved in a greater range of research-related activities).

[40] *See infra* Section II.A.

[41] *See infra* Section II.B.

[42] The quantity of off-label uses that are also new uses depends, in part, on how you define "new uses." Defining the question by reference to evidence makes all off-label uses new uses. If you define it by reference to *undiscovered* uses, then the overlap shrinks considerably. Discussions of new uses frequently fail to distinguish between these different senses of "new uses" and, therefore, tend not to see the similarities between the two problems. See *infra* Section II.C for a full discussion.

Recognizing the informational overlap enables this Article to make a second contribution: the entities best positioned to solve both Problems are not pharmaceutical companies, but providers—entities that actually provide services, such as hospitals, academic medical centers, health systems, healthcare networks, and even small office-based physician practices. The rationale for targeting providers is simple. They generate, or have the capability to generate, much of the needed post-market information about off-label drug prescriptions, use, and effects. And many providers, particularly large providers, have existing systems to monitor prescriptions and patients that can be leveraged to track and analyze off-label use. They also have institutional resources and knowledge that can be deployed to research off-label uses. The problem is that they lack incentives to do so.

Identifying the optimal set of incentives without further study is not possible. Instead, this Article seeks to illustrate how some incentives might capture innovative off-label uses, as well as data about off-label use and its effects. Four possible incentives—three ex ante (push) and one ex post (pull)—are reviewed. Two of the push incentives are government subsidies. The first is an existing government program that could be retooled for off-label use. The second is a new government subsidy to stimulate data collection, organization, and dissemination about off-label uses. The third push incentive is a tax credit. The fourth and final inducements discussed are variants of pull incentives that aim to produce data from clinical trials and observational studies: royalties, payments, or prizes for evidence development that result in FDA approval. The goal of Part III of the Article is not to assess which of these is best; rather, it's designed to show that there are a variety of policy levers that can be pulled to deliver the desired outcome: more safety and efficacy information about new and off-label uses.

Tackling the problems this way—by recognizing their informational commonality—has several significant benefits. First, it's efficient. Addressing both problems at the same time, with the same solution, costs less than addressing both at different times, with different solutions. Second, it's synergistic: addressing the Problem of New Uses will increase the number of better-supported uses and decrease the number of unsafe or ineffective off-label

uses.[43] The result is more uses supported by better evidence and fewer uses supported by weak or no evidence. At the same time, addressing the problem of off-label uses will help ameliorate the problem of new uses by identifying and researching innovative and valuable off-label uses. Third, it circumvents the problem of potentially negative information that typically dogs new uses.[44] Because drug manufacturers that conduct R&D of new uses risk discovering that the new use—or, worse still, the current approved use—is not safe and effective, they may be reluctant to do so.[45] Finally, this approach doesn't disturb existing incentives to pursue new drugs or new treatments. This is important because the existing incentive framework does produce valuable information, including some information about unapproved new uses of approved drugs.

Implementing new incentive structures, or leveraging old ones, entails costs—costs of legislative changes, of administration, of information collection and analysis. These costs are substantial. But they can't be properly known or weighed without further research. While that study can't be undertaken here, this Article seeks to achieve a more modest aim: to show that, whatever the costs, focusing attention on providers is one way to both identify new uses

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[43] *See infra* Section III.C. It will do this, however, only if it generates the kind of information needed for FDA approval. Even if this change doesn't result in an expanded indication, it would still provide much needed and valuable information about safety and efficacy (or at least effectiveness). Although the concepts of efficacy and effectiveness are not identical, I use them interchangeably throughout this Article. For a discussion of the FDA's trend toward accepting less traditional evidence, see Section II.C.

[44] *See* Rebecca S. Eisenberg & W. Nicholson Price, *Promoting Healthcare Innovation on the Demand Side*, 4 J.L. & BIOSCIENCES 3, 14 (2017) (describing opportunities to fund new uses).

[45] This worst-case scenario is what happened with the drug Vioxx (rofecoxib). The FDA approved Merck's NDA in 1999 for the treatment for osteoarthritis, acute pain, and primary dysmenorrhea. *See* Letter from Brian E. Harvey, Acting Division Director, U.S. Food & Drug Admin., to Dr. Evan M. Braunstein, Merck & Co., Inc. (Dec. 16, 2003), https://www.accessdata.fda.gov/drugsatfda_docs/nda/2003/021042_S024_VIOXXTM_APPROV.pdf. In 2000, Merck conducted research into whether the drug could prevent recurrent colon polyps. *See Vioxx (rofecoxib) Questions and Answers*, U.S. Food & Drug Admin, (Sept. 30, 2004), https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/vioxx-rofecoxib-questions-and-answers. The results of this new study showed that those who took the drug had an "increased risk [for] cardiovascular events such as heart attack and strokes." *Id.* Merck voluntarily pulled the drug from the market in 2004. Rebecca S. Eisenberg & W. Nicholson Price, *Promoting Healthcare Innovation on the Demand Side*, 4 J.L. & BIOSCIENCES 3, 10 (2017).

of approved drugs and generate better information about the safety and efficacy of off-label uses.

Part II of this Article explains the Problems of Off-Label Uses and the Problems of New Uses in detail. Both of these Problems, it shows, often overlap. In many cases, safety and efficacy information about off-label uses will be safety and efficacy information about new uses. And, in other cases, information about new uses of existing drugs will also be information about new, off-label uses that providers are testing in the field. In other words, there is a large informational overlap between the two Problems. Part III argues that providers are an untapped source of potential information that could ameliorate, if not solve, both Problems. Part IV describes potential provider-based incentives that would generate data to fill the informational deficit common to both Problems. While it doesn't offer one specific solution, it proposes several mechanisms—some old, some new, some push, some pull—to incentivize providers to produce, collect, analyze, and publish more information about innovative and existing off-label uses.

II. THE PROBLEM OF OFF-LABEL USES & THE PROBLEM OF NEW USES

The purpose of this Part is to explain both Problems and how they are related to the same information. Section A explains the Problem of Off-Label Uses, why it's a problem, and how scholars have proposed to rectify it. Section B follows the same structure with respect to the Problem of New Uses. Section C shows how these two Problems often stem from a lack of identical information. This informational overlap naturally suggests a solution that focuses on the entities best positioned to collect the needed information: providers.

A. THE PROBLEM OF OFF-LABEL USES

Patients with diseases that lack FDA-approved treatments still need access to drugs that might help them. Prescribing drugs under these conditions, however, is often risky because the safety and efficacy data are limited. This is, as I explain below, a problem of

information. And most scholars have tried to solve it by limiting off-label use.

1. Off-Label Use. Off-label use occurs when a physician prescribes an approved drug for an unapproved use.[46] Approved drugs are those that the FDA has decided, at the insistence of pharmaceutical companies, are safe and effective for an intended use. Without this approval, drugs generally can't reach the market.[47] To obtain approval, a drug company must demonstrate to the FDA that a drug is safe and effective for an intended use by "substantial evidence."[48] It begins this process by filing an Investigational New Drug Application (IND),[49] which shows the

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[46] Off-label uses are also referred to in the literature as "unapproved" uses. *See, e.g.*, M.M. Saiyed, P.S. Ong & L. Chew, *Off-Label Drug Use in Oncology: A Systematic Review of Literature*, 42 J. CLINICAL PHARMACY & THERAPEUTICS 251, 256 (2017). When physicians prescribe an *unapproved drug*—a drug not approved for any use by the FDA—the use is *unlicensed*. *Id.* at 251. Both off-label and unapproved uses are different from *compassionate use* or *expanded access*, which occurs when the FDA temporarily allows patients with serious conditions to access "investigational medical products . . . outside of clinical trials when no comparable or satisfactory alternative therapy options are available." *Expanded Access*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/news-events/public-health-focus/expanded-access (last updated Mar. 23, 2021).

[47] *See* 21 U.S.C. § 355(a) ("No person shall introduce or deliver for introduction into interstate commerce any new drug, unless an approval . . . is effective with respect to such drug."); *see also Enforcement Activities, Unapproved Drugs*, U.S. FOOD & DRUG ADMIN. (June 2, 2021), https://www.fda.gov/drugs/enforcement-activities-fda/unapproved-drugs (last visited Apr. 26, 2022) ("Federal law requires all new drugs in the U.S. be shown to be safe and effective for their intended use prior to marketing."). *But see id.* ("FDA permits some unapproved prescription drugs to be marketed [under three conditions].").

[48] *See* 21 U.S.C. § 355(d) ("[T]he term 'substantial evidence' means evidence consisting of adequate and well-controlled investigations . . . by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded . . . that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof."); 21 C.F.R. § 314.50(d)(5)(v) (2020) (setting forth requirements for the effectiveness of data); 21 C.F.R. § 314.126 (2020) (stating the purpose of conducting clinical drug investigations and describing the characteristics of a well-controlled study).

[49] *See* 21 C.F.R. § 312.23 (2020) (requiring sponsors intending to conduct clinical investigations to submit an IND with specific content and format requirements); PETER BARTON HUTT, RICHARD A. MERRILL & LEWIS A. GROSSMAN, FOOD AND DRUG LAW 674 (4th ed. 2014) (explaining that "a manufacturer must first obtain FDA approval of a new drug application" and that the FDA created the IND procedure to implement the congressional exemption allowing new drug sponsors "to carry out the clinical testing necessary to support FDA approval of an NDA").

FDA that the target drug has undergone preclinical testing in animals.[50] Once the IND goes into effect,[51] there are usually three phases of review.[52] In Phase I,[53] the company conducts clinical trials with a small number of healthy volunteers to determine how the drug works in the body, its relative safety, and, preliminarily, its effectiveness.[54] Phase II studies are directed toward efficacy.[55] They are usually somewhat larger than Phase I studies, up to a few hundred participants, and are controlled using the relevant patient population.[56] Once a sponsor successfully completes Phase I and II studies, it enters Phase III, conducting larger clinical trials to determine the drug's overall safety and efficacy.[57] A drug sponsor can and usually does consult with the FDA during any Phase, but it is not required to do so.[58] After completing all three Phases, the drug sponsor can submit a new drug application (NDA) based on the results of its clinical trials.[59] In the NDA, the sponsor must also make various filings and attestations about the drug and its

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[50] *See* 21 C.F.R. § 312.23(a)(8) (2020) (dictating that the IND plan should include "information about pharmacology and toxicological studies of the drug involving laboratory animals"). These tests must have been conducted using good laboratory practices. 21 C.F.R. § 58 (2020); *see also* CTR. FOR DRUG EVALUATION & RSCH., U.S. DEP'T OF HEALTH & HUM. SERVS., GUIDANCE FOR INDUSTRY, INVESTIGATORS, AND REVIEWERS: EXPLORATORY IND STUDIES 2–3 (2006) [hereinafter IND GUIDANCE], https://www.fda.gov/files/Guidance-to-Industry-and-Reviewers---Exploratory-IND-Studies-%28PDF%29.pdf (stating that an IND containing information on "any risks anticipated based on the results of pharmacologic and toxicological data collected during studies of the drug in animals" must be submitted before human studies can begin); HUTT ET AL., *supra* note 49, at 671 ("During preclinical drug development, a sponsor evaluates the drug's toxic and pharmacologic effects through *in vitro* and *in vivo* laboratory animal testing.").

[51] The IND will go into effect unless the FDA issues a clinical hold within 30 days of receiving the IND. 21 C.F.R. § 312.40(b)(1) (2020).

[52] 21 C.F.R. § 312.21 (2020).

[53] In 2006, the FDA released guidance on so-called "Phase 0" studies, which were intended to act as a "exploratory IND stud[ies]" occurring very early in Stage 1. IND GUIDANCE, *supra* note 50, at 1.

[54] 21 C.F.R. § 312.21(a) (2020).

[55] *See* 21 C.F.R. § 312.21(b) (2020) ("Phase 2 includes controlled clinical studies conducted to evaluate the effectiveness of the drug for a particular indication . . . .").

[56] 21 C.F.R. § 312.21(b) (2020).

[57] 21 C.F.R. § 312.21(c) (2020).

[58] *See The Drug Development Process, Step 3: Clinical Research*, U.S. FOOD & DRUG ADMIN. (Jan. 4, 2018), https://www.fda.gov/patients/drug-development-process/step-3-clinical-research.

[59] 21 C.F.R. § 314.105(c) (2020).

manufacturing practices.[60] The purpose of an NDA is to convince the FDA that the drug is safe and effective for its intended use.[61]

Drug makers expend large quantities of time and money building their cases for the FDA, most of which are unpersuasive.[62] The most recent estimates peg new drug development capitalized costs at between $1,395 million and $2,558 million,[63] a figure that has grown continually since Congress implemented the modern regulatory regime in 1962.[64] If a drug sponsor convinces the FDA to approve a "new drug," its approval is limited to using the drug for a specific

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[60] 21 C.F.R. § 314.50 (2020).

[61] *See The Drug Development Process, Step 4: FDA Drug Review*, U.S. FOOD & DRUG ADMIN. (Jan. 4, 2018), https://www.fda.gov/patients/drug-development-process/step-4-fda-drug-review. In some cases, sponsors conduct Phase IV studies. These studies include post-marketing surveillance imposed by the FDA and "real world" tests of a drug after it hits the market. *See* Viraj Suvarna, *Phase IV of Drug Development*, 1 PERSPS. CLINICAL RSCH. 57, 57–58 (2010).

[62] *See* Joseph A. DiMasi, Henry G. Grabowski & Ronald W. Hansen, *Innovation in the Pharmaceutical Industry: New Estimates of R&D Costs*, 47 J. HEALTH ECON. 20, 23 (2016) [hereinafter DiMasi et al., *Innovation in the Pharmaceutical Industry*] (estimating an 11.83% overall probability that a drug that enters clinical testing will eventually be approved); J.A. DiMasi, L. Feldman, A. Seckler & A. Wilson, *Trends in Risks Associated with New Drug Development: Success Rates for Investigational Drugs*, 87 CLINICAL PHARMACOLOGY & THERAPEUTICS 272, 276 (2010) ("For self-originated new drugs that first entered clinical testing in 1993–2004 and were observed through mid-2009, the results indicated that approximately one in six drugs that enter the clinical testing pipeline will eventually obtain approval for marketing in the United States."); Henry Grabowski, *Increasing R&D Incentives for Neglected Diseases: Lessons from the Orphan Drug Act*, *in* INTERNATIONAL PUBLIC GOODS AND TRANSFER OF TECHNOLOGY UNDER A GLOBALIZED INTELLECTUAL PROPERTY REGIME 457, 462 (Keith E. Maskus & Jerome H. Reichman eds., 2005) ("[I]t it takes several hundred million dollars to discover, develop, and gain regulatory approval for a new medicine."). *But see* Dan L. Burk & Mark A. Lemley, *Levers in Patent Law*, 89 VA. L. REV. 1575, 1616 & n.131 (2003) (noting that the $800 million R&D figure is "almost certainly inflated" because it includes sizeable advertising budgets).

[63] *See* DiMasi et al., *Innovation in the Pharmaceutical Industry*, *supra* note 62, at 26 (finding fully capitalized total costs of $2558 million per approved new drug during the 2000s to mid 2010s); Steve Morgan, Paul Grootendorst, Joel Lexchin, Colleen Cunningham & Devon Greyson, *The Cost of Drug Development: A Systematic Review*, 100 HEALTH POL'Y 4, 7 tbl.1 (2011) (compiling studies and total estimates of cost of drug development); Joseph A. DiMasi, Ronald W. Hansen & Henry G. Grabowski, *The Price of Innovation: New Estimates of Drug Development Costs*, 22 J. HEALTH ECON. 151, 162 tbl.1 (2003) [hereinafter DiMasi et al., *The Price of Innovation*] (finding an average out-of-pocket clinical period cost for investigational compounds of $60.6 million).

[64] *See, e.g.*, DiMasi et al., *The Price of Innovation*, *supra* note 63, at 154 fig.1 (displaying the upward trend in inflation-adjusted industry R&D expenditures from 1963 to 2000).

indication (condition), at a specific dose, by a specific route of administration, often in a specific population.[65] By law, all of this information must appear on the drug's labeling.[66] Drug manufacturers are not permitted to market their products in a manner inconsistent with the approved NDA or drug labeling.[67]

But physicians aren't bound by labels. Because the FDA doesn't regulate the practice of medicine,[68] physicians are free to prescribe any approved drug for a different indication, at a different dose, by a different route of administration, in a different patient

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[65] *See* 21 U.S.C. § 355 (2018) (regulating "new drugs"); 21 C.F.R. §310.3(g)–(h) (2020) (defining "new drug substance" and establishing that the newness of a drug may arise from, among other reasons,"[t]he newness of a dosage, or method or duration of administration or application, or other condition of use prescribed, recommended, or suggested in the labeling of such drug").

[66] 21 C.F.R. §§ 201.50, 201.51, 201.55, 201.56, 201.57 (2019) (setting out labeling requirements for a drug's statement of identity, net quantity, dosage, and other content and format standards). *But see id.* § 201.58 (providing that applicants can request the FDA to waive labeling requirements).

[67] *See, e.g.*, 21 U.S.C. § 355(a) (2018) (requiring approval for new drugs); 21 U.S.C. § 352(a)(1) (2018) (requiring drugs to conform to labeling approved under 21 U.S.C. § 355); 21 C.F.R. § 201.100(c)(1) (2019) (requiring labels for prescription drugs for human use to bear adequate information for use); 21 U.S.C. § 321(m) (2018) (defining labeling). For more about how the FDA prosecutes off-label regulation, see David A. Simon, Evidence-Based Regulation of Off-Label Information 7–8 (Oct. 18, 2021) (unpublished manuscript) (on file with author) [hereinafter Simon, *Off-Label Information*] ("Beyond labeling, the FDA can prosecute claims of off-label promotion using its power to regulate drug advertising."). *See also* David A. Simon, *Trademark Law & Consumer Safety*, 72 FLA. L. REV. 673, 711 (2020) [hereinafter Simon, *Consumer Safety*] (explaining that since Congress expanded the power and scope of the FDA's authority in 2007, the FDA has increasingly used trademark law to regulate both prescription and over-the-counter drugs).

[68] *See FDA's Role in Regulating Medical Devices*, U.S. FOOD & DRUG ADMIN. (Aug. 31, 2021), https://www.fda.gov/medical-devices/home-use-devices/fdas-role-regulating-medical-devices ("FDA regulates the sale of medical device products . . . and monitors the safety of all regulated medical products. . . . The FDA does not have the authority to[] [r]egulate a physician's or nurse's practice.").

population.[69] When they do, they are prescribing "off-label."[70] They are prescribing an approved drug for a *use* that the FDA did not approve.[71] Although what counts as off-label use isn't static[72] or uniformly defined,[73] this description is useful and precise enough for purposes of this Article.[74]

Physicians prescribe drugs off-label for various reasons. Sometimes there are no front-line treatments for a particular condition.[75] So the physician may try an approved medication for another condition by using it off-label in an attempt to provide relief

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[69] *See* Philip M. Rosoff & Doriane Lambelet Coleman, *The Case for Legal Regulation of Physicians' Off-Label Prescribing*, 86 NOTRE DAME L. REV. 649, 650, 661–64 (2011) ("Typical off-label uses (OLU) include promoting, prescribing, and ingesting substances for conditions other than those for which they were approved, in higher- or lower-than-indicated dosages, and in populations other than those in which they were tested."); *see also* U.S. FOOD & DRUG ADMIN., "OFF-LABEL" AND INVESTIGATIONAL USE OF MARKETED DRUGS, BIOLOGICS, AND MEDICAL DEVICES: GUIDANCE FOR INSTITUTIONAL REVIEW BOARDS AND CLINICAL INVESTIGATORS (1998), https://www.fda.gov/regulatory-information/search-fda-guidance-documents/label-and-investigational-use-marketed-drugs-biologics-and-medical-devices ("Good medical practice and the best interests of the patient require that physicians use legally available drugs, biologics and devices according to their best knowledge and judgement. If physicians use a product for an indication not in the approved labeling, they have the responsibility to be well informed . . . .").

[70] Even outside the United States, the definition is largely the same. *See, e.g.*, Marc Dooms, David Cassiman & Steven Simoens, *Off-Label Use of Orphan Medicinal Products: A Belgian Qualitative Study*, 11 ORPHANET J. RARE DISEASES 1, 1 (2016) ("Off-label use of a medicinal product entails the intentional use of the medicinal product for any indication, population, dosage, administration route or treatment duration other than that approved by a country's regulatory authority.").

[71] Not all off-label uses are reimbursed either by private insurance or by the Centers for Medicare & Medicaid Services (CMS). *See* Simon, *Off-Label Information*, *supra* note 67, at 41.

[72] *See* Saiyed et al., *supra* note 46, at 256 ("Prescribing practices reported as 'off-label' in the literature years back might not be considered off-label today due to changes in prescribing information.").

[73] *See* Joana Magalhães et al., *Use of Off-Label and Unlicenced Drugs in Hospitalised Paediatric Patients: A Systematic Review*, 71 EUR. J. CLINICAL PHARMACOLOGY 1, 8 (2015) (listing different methodologies of determining what off-label use entails, stating "there was no consensus on a common definition of off-label and unlicensed drugs").

[74] An off-label use isn't an "improper, illegal, contraindicated, or investigational use." Xiulu Ruan & Alan David Kaye, *Off-Label Prescribing: Justified or Not?*, 31 AM. J. MED. QUALITY 101, 101 (2016).

[75] *See, e.g.*, Mahmoud Chehab, Alosh Madala & J.C. Trussell, *On-Label and Off-Label Drugs Used in the Treatment of Male Infertility*, 103 FERTILITY & STERILITY 595, 595 (2015) (describing the necessity of off-label treatments for male infertility without known cause).

for a patient where there might otherwise be none.[76] Other times, clinical data may not exist for the *population* the doctor treats despite using the medication to treat the same *condition* as one listed on the approved labeling.[77] This is common in pediatric practices, for example, because children often can't be included in study populations for ethical reasons.[78] Physicians treating these patient populations often *must* prescribe drugs off-label—the patient population is different—because sponsors can't or won't conduct the clinical trials necessary for FDA approval.[79] On occasion, as well, an off-label use may be the standard of care to treat a particular condition.[80] Doctors, for example, frequently

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[76] *See, e.g.*, Svetlana Goločorbin Kon, Ivana Iličkoviĉ & Momir Mikov, *Reasons for and Frequency of Off-Label Drug Use*, 68 MEDICINSKI PREGLED 35, 38 (2015) (noting that the lack of effective and safe treatments is a primary reason for off-label use).

[77] *See, e.g.*, Martha M. Rumore, *Medication Repurposing in Pediatric Patients: Teaching Old Drugs New Tricks*, 21 J. PEDIATRIC PHARMACOLOGY & THERAPEUTICS 36, 37 (2016). *But see* 26 U.S.C. § 45(e)(11)(C) (providing tax credits for clinical testing expenses for certain drugs); *infra* Section III.D (discussing how tax incentives can induce providers to institute off-label use).

[78] *See, e.g.*, Marc A. Rodwin, *Rooting out Institutional Corruption to Manage Inappropriate Off-Label Drug Use*, 41 J.L. MED. & ETHICS 654, 655 (2013) ("[R]esearch protocol typically excludes children . . . who are more vulnerable to adverse drug reactions (which might reflect badly on the drug) . . . ."); Jennifer L. Herbst, *How Medicare Part D, Medicaid, Electronic Prescribing, and ICD-10 Could Improve Public Health (But Only If CMS Lets Them)*, 24 HEALTH MATRIX 209, 241 (2014) [hereinafter Herbst, *Medicare Part D*] ("[M]any of the patients historically covered by Medicaid—children . . . are also often excluded from clinical trials for both ethical and practical reasons."); *id.* at 241–43 (describing the benefits of private insurer, Medicare, and Medicaid databases providing "a broader cross-section of the population").

[79] The Best Pharmaceuticals for Children Act (BPCA) has changed this somewhat, but sponsors are still reluctant to conduct trials on children below the age of 12. *See* 21 U.S.C. §§ 355a, 355c (detailing the application and approval process for "[p]ediatric studies of drugs" and "[r]esearch into pediatric uses for drugs and biological products"); Rumore, *supra* note 77, at 36–37, 37 tbl.1 (discussing several reasons why companies are reluctant to conduct research in the pediatric population, such as how the FDA does not mandate pediatric ages to be tested, indicating some medications received exclusivity by testing in 12- to 17-year-olds, and listing various provisions of the BPCA).

[80] See Jennifer L. Herbst, The Short-Sighted Value of Inefficiency: Why We Should Mind the Gap in the Reimbursement of Outpatient Prescription Drugs, 2 CASE W. RES. J.L. TECH. & INTERNET 1, 3 (2011) [hereinafter Herbst, Short-Sighted] ("Off-label use of prescription drugs . . . occasionally reflects the recognized standard of care for a disease or condition.").

prescribe amitriptyline[81] to treat neuropathic pain[82] even though it is approved only to treat depression.[83]

Prescribing drugs off-label is considered an essential part of medicine for several reasons. First, it allows physicians to tailor treatment choices to individual patients.[84] Second, off-label use enables physicians to treat patients when, as noted above, no on-label treatment options exist, or where the off-label use is the standard of care.[85] Finally, and this is a point I return to in Section II.C, off-label prescribing is a source of innovation in drug use and development.

2. The Problem of Off-Label Uses as an Informational Problem. Although off-label uses are important, they can also be riskier than on-label uses. Off-label uses may not be supported by the same kind or quantity of evidence as on-label uses.[86] Some may be supported by a single case report or a series of them or by varying kinds of

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[81] Joseph Acton, John E. McKenna & Ronald Melzack, *Amitriptyline Produces Analgesia in the Formalin Pain Test*, 117 EXPERIMENTAL NEUROLOGY 94–95 (1992) (describing that Amitriptyline is a drug designed to treat depression that has been shown to have other uses). Another example is chenodeoxycholic acid (Chenodiol), described *supra* note 30.

[82] *See, e.g.*, Acton et al., *supra* note 81, at 94–95 ("Amitriptyline . . . [is] often extremely effective in relieving various forms of chronic pain."); Kalso Eija, Tasmuth Tiina & Neuvonen Pertti J, *Amitriptyline Effectively Relieves Neuropathic Pain Following Treatment of Breast Cancer*, 64 PAIN 293, 301 (1995) ("The number of daily activities being disturbed by pain and the effect of pain on daily life were significantly reduced with amitriptyline."); R. Andrew Moore, Sheena Derry, Dominic Aldington, Peter Cole & Phillip J. Wiffen, *Amitriptyline for Neuropathic Pain in Adults*, COCHRANE DATABASE SYSTEMATIC REVS. 1, 2 (2015), http://doi.wiley.com/10.1002/14651858.CD008242.pub2 ("Amitriptyline is commonly used to treat neuropathic pain conditions . . . . "). *But see* Diana D. Cardenas, Catherine A. Warms, Judith A. Turner, Helen Marshall, Marvin M. Brooke & John D. Loeser, *Efficacy of Amitriptyline for Relief of Pain in Spinal Cord Injury: Results of a Randomized Controlled Trial*, 96 PAIN 365, 372 (2002) ("Possibly amitriptyline might be more efficacious for certain types of pain, but our exploratory analyses did not reveal such effects. . . . ").

[83] The FDA approved amitriptyline (trade name Elavil) for depression on April 7, 1961 in NDA 012703 (approval for new molecular entity). *See* Food and Drug Admin., Determination that Elavil (Amitriptyline Hydrochloride) Oral Tablets, 10, 25, 50, 75, 100, and 150 Milligrams, Were Not Withdrawn from Sale for Reasons of Safety or Effectiveness, 82 Fed. Reg. 49,032, 49,033 (Oct. 23, 2017) (describing how Elavil was "initially approved on April 7, 1961" for "relief of symptoms of depression").

[84] *See infra* note 186.

[85] *See supra* notes 75–76 and accompanying text.

[86] *See, e.g.*, DAVID CAVALLA, OFF-LABEL PRESCRIBING: JUSTIFYING UNAPPROVED MEDICINE 8–11 (2015) (discussing how "the prescription of a drug in an off-label fashion, based as it is on limited evidence, does not itself result in the enlargement of the evidence base").

observational studies, clinical trials, or meta-analyses. One study even claims to show that a large portion of off-label uses lacks any evidentiary basis.[87] If true, this means limited or no safety and efficacy data support existing prescribing practices. If limited data do exist, they may be confined to closely related indications or consist of limited reporting of use or case studies in the literature.

This lack of information poses serious risks to, and imposes real monetary costs on, patients who fall outside of the approved labeling. Off-label use increases the chance of adverse events.[88] These risks increase as evidence for the relevant use thins out.[89] One reason for this is that drug effects are hard to predict. Even the same dose of a drug can have wildly different effects in disparate patient populations. Children, for example, metabolize drugs differently than adults, complicating attempts by physicians to extrapolate dosage from one to the other.[90] A lack of studies involving children, however, makes extrapolation necessary.[91] Patients also may have comorbidities, or simply different genotypes, that make adverse reactions more or less likely.[92] In psychiatry, where off-label use is prevalent, the risk is not merely using a drug with limited evidence but failing to treat the underlying behavioral

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[87] *See* David C. Radley, Stan N. Finkelstein & Randall S. Stafford, *Off-label Prescribing Among Office-Based Physicians*, 166 ARCHIVES INTERNAL MED. 1021, 1025 (2006) ("[W]e found that about 21% of all estimated uses for commonly prescribed medications were off-label, and that 15% of all estimated uses lacked scientific evidence of therapeutic efficacy.").

[88] Some studies have reported higher rates of adverse events for off-label uses than on-label ones—rates that increase as the evidentiary support for the off-label use decrease. *See, e.g.,* Tewodros Eguale, David L. Buckeridge & Aman Verma, *Association of Off-label Drug Use and Adverse Drug Events in an Adult Population*, 176 JAMA INTERNAL MED. 55, 61 (2016) (concluding based on a study comparing on-label adverse drug effects to off-label adverse drug effects that off-label drug use increases the risk for adverse drug effects); *see also* CAVALLA, *supra* note 86, at 9–10 (noting that increased risk for adverse drug reactions also applies to younger pediatric patients and for psychiatric care).

[89] *See* Eguale, *supra* note 88, at 61 ("Off-label drug use, and particularly off-label use without strong scientific evidence, is a risk factor for [adverse drug effects].").

[90] *See* J.D. Momper, Y. Mulugeta & G.J. Burckart, *Failed Pediatric Drug Development Trials*, 98 CLINICAL PHARMACOLOGY & THERAPEUTICS 245, 245 (2015).

[91] *See* CAVALLA, *supra* note 86, at 9, 13 (noting a lack of understanding of off-label use for pediatric patients and reviewing prevalence of off-label use in pediatric practices and finding rates as high as 76%).

[92] *See, e.g.*, Eguale, *supra* note 88, at 57 (including "age and measures of comorbidity" in a study "because older patients and those with more than 1 comorbidity may have a higher risk for" adverse drug effects (footnotes omitted)).

problem.[93] Because of these risks, and the costs associated with improper prescriptions, almost every commentator discussing the topic is concerned with the relative safety and efficacy of off-label uses.[94]

The difficulty presented by off-label uses, as Ryan Abbott and Ian Ayres note, results from an information deficit: because off-label uses generally are not supported by the same evidence as approved uses, patients taking a drug off-label may be exposed to risks without knowing whether a drug is safe and effective.[95] The problem is exacerbated by features of patent law that fail to provide adequate incentives to generate the clinical trial data needed to fill this gap entirely.[96] The result is the Problem of Off-Label Uses: off-label use occurs necessarily and frequently, but there may be insufficient information about the safety and efficacy of these uses. In other words, there often may be insufficient information about the type, frequency, and effects of off-label use.

Because the Problem of Off-Label Uses results from lack of information, some scholars have proposed to solve it using more data.[97] Abbott and Ayres, for example, focus on a centralized, top-

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[93] *See* CAVALLA, *supra* note 86, at 12–13 (describing how in cases of depression, higher off-label dosages may be used with the desire to ensure greater efficacy, but that use could cause various safety issues).

[94] *See, e.g.*, Radley et al., *supra* note 16, at 1021 ("Although this practice provides a pathway to innovation in clinical practice, it raises key concerns about risks to patients and costs to the health care system."); CAVALLA, *supra* note 86, at 13 ("In most cases . . . , adequate research evidence to support off-label prescribing is lacking."); Abbott & Ayres, *supra* note 19, at 388 (noting a lack of research for off-label uses).

[95] *See* Abbott & Ayres, *supra* note 19, at 388; 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, 65 (2008) ("[T]he prevalence of off-label prescribing is a manifestation both of learning patterns in the medical profession and deficiencies in the production and dissemination of clinical knowledge."); *id.* at 82–83 (noting that safety concerns from lack of information are prevalent for all drugs, not just off-label uses); *see also* Evans, *infra* note 124, at 439–50 (explaining that a drug's safety and efficacy profile cannot be known until the drug has been on the market for a sufficient period of time due to the ways premarket safety trials are conducted); Louis Lasagna, *Discovering Adverse Drug Reactions*, 249 JAMA 2224, 2225 (1983) (stating that reporting by physicians after original FDA approval is the most important way that drug manufactures and the FDA can learn about long-term adverse drug effects).

[96] *See infra* Sections III.A–B.

[97] *See* Abbott & Ayres, *supra* note 19, at 399. As noted below, not all proposals to curb off-label use focus on this information deficit. *See infra* note 101; *see also* CAVALLA, *supra* note

down approach that relies on the FDA to gather, police, evaluate, and communicate information about off-label uses.[98] This includes the creation of a new labeling system.[99] George Horvath argues for a skinny version of Abbott and Ayres' proposal, where the volume of off-label sales triggers manufacturer obligations to disclose off-label uses.[100] Others, such as David Kwok and Mark Rodwin, view off-label prescribing as a practice to be curbed and propose various legal

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86, at 173–74 (arguing for higher professional standards, changing reimbursement incentives, and tracking off-label outcomes); Muriel R. Gillick, *Controlling Off-Label Medication Use*, 150 ANNALS INTERNAL MED. 344, 345–46 (2009) (arguing that off-label use should be regulated in the same manner as medical devices, using a two-step review process, including a CMS National Coverage Determination, for drugs that are expensive and risky); Ralph F. Hall & Elizabeth S. Sobotka, *Inconsistent Government Policies: Why FDA Off-Label Regulation Cannot Survive First Amendment Review Under* Greater New Orleans, 62 FOOD & DRUG L.J. 1, 45–46 (2007) (canvassing a variety of approaches to curb off-label prescribing, including a reimbursement ban, a prescription ban, preemption of product liability cases for on- but not off-label uses, tax incentives and rebates for expanded indications, greater patent exclusivity for on- and off-label uses, and mandating sNDAs for "for products the manufacturer knows are being used in any significant off-label manner"); United States v. Caronia, 703 F.3d 149, 168 (2d Cir. 2012) ("To minimize off-label use, or manufacturer evasion of the approval process for such use, the government could create other limits, including ceilings or caps on off-label prescriptions.").

[98] *See* Abbott & Ayres, *supra* note 19, at 399–412. (advocating for a new coding system for off-label uses). Similar proposals with respect to labeling have been developed in other countries as well. *See, e.g.*, Hanbin Wu & Gao Wu, *Strategy to Address Innovative Off-Label Medication Use in China: Grading Management*, 70 EUR. J. CLINICAL PHARMACOLOGY 1271, 1272 (2014) (arguing for a five-category system to indicate the nature of the off-label prescribing in China).

[99] *See* Abbott & Ayres, *supra* note 19, at 412–17 (providing an overview of the proposed "tiered labeling system"). But it is not clear how much this would help. *See* CAVALLA, *supra* note 86, at 11 (noting a recent study in the United States showing that "widespread ignorance of what drugs were actually approved for"); Donna T. Chen, Matthew K. Wynia, Rachael M. Moloney & G. Caleb Alexander, *U.S. Physician Knowledge of the FDA-Approved Indications and Evidence Base for Commonly Prescribed Drugs: Results of a National Survey*, 18 PHARMACOEPIDEMIOLOGY & DRUG SAFETY 1094, 1099 (2009) (finding that physicians misconstrue the meaning of FDA approval in determining a drug's efficacy for a certain use); Johnson, *supra* note 95, at 79 (reviewing literature in which physicians ignore warning letters and black box warnings).

[100] George Horvath, *Off-Label Drug Risks: Toward a New FDA Regulatory Approach*, 29 ANNALS HEALTH L. & LIFE SCIS. 101, 127 (2020); *see also* Philip M. Rosoff & Doriane Lambelet Coleman, *The Case for Legal Regulation of Physicians' Off-Label Prescribing*, 86 NOTRE DAME L. REV. 649, 652 (2011) (describing four categories of off-label use (OLU): "OLU justified by high-quality evidence, OLU justified by some but not high-quality evidence, OLU justified by the need or desire to innovate, and unjustified OLU").

mechanisms to put financial pressure on drug manufacturers to do so.[101] While each of these proposals has merit, they all approach the Problem of Off-Label Uses as a standalone challenge. And they aim to meet that challenge—however they frame it—by beefing up existing regulatory frameworks. By doing so, they fail to capitalize on the possibility of solving the Problem a different way, as well as the opportunity to simultaneously address a different problem: the Problem of New Uses.[102]

B. THE PROBLEM OF NEW USES

New uses of old drugs are sorely needed. Not only are R&D costs for novel drug compounds increasing, but total investment in drug development has also consistently declined since 1950.[103] Both

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[101] *See* David Kwok, *Controlling Excessive Off-Label Medicare Drug Costs Through the False Claims Act*, 27 HEALTH MATRIX 185, 211, 220 (2017) (arguing for reimbursement caps and noting that "[r]egardless of the precise optimal reimbursement rate, all reform proposals hinge upon one critical piece of information: tying patient indication to the prescription"); *id.* at 209, 219–20 (proposing using the False Claims Act's civil liability claw-back mechanism to lower drug prices for off-label prescriptions reimbursed under Medicare Part D, capping off-label reimbursement "at a rate tied to the competitive, patent-protected market for treatment of the condition"); Rodwin, *supra* note 78, at 659 (proposing making off-label prescribing more expensive for manufacturers so that they will discourage the practice); *see also* Herbst, *Short-Sighted*, *supra* note 80, at 4 (proposing a regulatory fix by requiring "diagnosis codes on claims submitted for federal reimbursement of outpatient prescription drugs under the Medicare Part D and Medicaid programs"); Herbst, *Medicare Part D*, *supra* note 78, at 214, 223 (arguing that CMS should require diagnostic codes for all prescriptions as a condition of reimbursement but not for coverage determinations).

[102] While some legal scholars have noted in passing the innovative nature of off-label prescribing, most proposals focus on restricting off-label prescribing to limit risks rather than to capture and cultivate the effects of off-label prescribing when it occurs. *See, e.g.*, Abbott & Ayres, *supra* note 19, at 390–91 (contending that "[o]ff-label drug use . . . may also serve as a pathway to innovation" and noting the failure to capture this information but focusing on problems with current off-label use and marketing); Rodwin, *supra* note 78, at 659 (proposing a limit to off-label prescribing by changing pharmaceutical firms' economic incentives); Kwok, *supra* note 101, at 188 (putting forth a proposal of a new "theoretical reimbursement framework that eliminates this distortion and unfairness by capping off-label reimbursements at a competitive level"); Horvath, *supra* note 100, at 127 (proposing that a manufacturer should have a duty to disclose available clinical data "once off-label prescriptions account for a certain volume or percentage of a drug's total prescriptions").

[103] *See* Jack W. Scannell et al., *Diagnosing the Decline in Pharmaceutical R&D Efficiency*, 11 NATURE REVS. DRUG DISCOVERY 191, 191 (2012) (showing that the number of new FDA drugs approved "per billion US dollars of R&D spending in the drug industry has halved

increased R&D costs and decreased spending on R&D reduce the overall number of available new drugs.[104] As investments in new drugs become riskier, firms take fewer chances for higher returns.[105] When investments are successful, they are expected to generate large profits, which also translates into high drug prices.

With costs rising and investment declining, new uses of approved drugs are particularly attractive. Compared to new drug development, new use development is dirt-cheap.[106] Thrift is made possible by existing knowledge about how to manufacture the drug, as well as information about its safety, toxicity, pharmacokinetics, mechanism of action, and even its effect on gene expression, all of which reduce the total investment required to bring the drug to market.[107] "Big Data" promises to reduce these costs even further by screening various uses before they are tested in a lab or clinical trial.[108] But they are difficult to commercialize. Traditional means of creating incentives for drug research and development—patent monopoly and market exclusivity—do not work as well for new uses of old drugs, giving rise to the Problem of New Uses.

This Section explains why. It shows that this problem, like the Problem of Off-Label Uses, is also one of information. The problem is not, in other words, that we don't have the right tools; it's that we aren't using them because we've relied on the wrong kind of entity (the pharmaceutical company), or at least wrongly relied *primarily*

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approximately every [nine] years since 1950" and that costs have been growing steadily ever since). In a 2021 paper, Katherine Liddell and John Liddicoat show that government investment in new uses has far eclipsed private sector innovation. *See* Johnathon Liddicoat, Kathleen Liddell, Mateo Aboy & Jakob Wested, *Has the EU Incentive for Drug Repositioning Been Effective? An Empirical Analysis of the "+1" Regulatory Exclusivity,*52 INT'L REV. INTELL. PROP. & COMPETITION L. 825, 826–27 (2021) (studying the effectiveness of European incentives to marketing authorization holders to create new uses).

[104] *See* Scannell et al., *supra* note 103, at 191 ("R&D efficiency, measured simply in terms of the number of new drugs brought to market . . . has declined fairly steadily.").

[105] *See id.* at 193–94 ("Progressive lowering of the risk tolerance of drug regulatory agencies obviously raises the bar for the introduction of new drugs . . . .").

[106] *See* Roin, *supra* note 26, at 4–5 (stating that developing a new drug costs an estimated $1.2 billion while repurposing a drug only costs $300 million on average).

[107] *See id.* at 5, 21, 42, 46 (contending that new use development is much quicker because of the familiarity with the drug).

[108] *See, e.g.*, Sudeep Pushpakom et al., *Drug Repurposing: Progress, Challenges and Recommendations*, 18 NATURE REVS. DRUG DISCOVERY 41, 55 (2019) (discussing the benefits of big data).

on that entity, to produce the needed information. To get there, Subsections 1 and 2 briefly explain how patent law and market and data exclusivity fail to incentivize R&D of new uses of old drugs. Subsection 3 then explains how these two seemingly different problems often arise because of the same informational deficit: lack of information about the use and effects of drugs off-label.

1. Patent Law. Patent law, in particular, has played a critical role in new drug pharmaceutical development. It encourages drug development by dangling the prospect of a twenty-year legal monopoly for any novel, useful, and non-obvious invention.[109] Patent owners can use this to prevent others from making, using, offering to sell, or selling the patented invention.[110] In return, inventors must disclose what they patented.[111]

Merely obtaining a patent on a novel drug compound isn't, by itself, enough to generate profit. That's because drug companies must first obtain FDA approval to market a drug. Without this approval, a patented drug can't be sold to consumers. Patents, in other words, are options to commercialize the drug.[112] Exercising these options requires significant investment in research and clinical trials—neither of which guarantees market success or even market entry.[113] Just to reach the market, the drug maker must use this data to convince the FDA that the drug is safe and effective.[114] Both the research and regulatory review process can last many years, and most trials peter out before Phase III trials take place.[115]

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[109] *See* 35 U.S.C. §§ 101–02(a), 103,154(a)(2); *see also* U.S. CONST. art. I, § 8, cl. 8 ("To promote the Progress of Science and useful Arts, securing for limited Times to Authors and Inventors the exclusive Right to their respective Writings and Discoveries . . . .").

[110] *See* 35 U.S.C. § 271(a) (setting forth the requirements for patent infringement).

[111] *See* CRAIG ALLEN NARD, THE LAW OF PATENTS 3 (4th ed. 2017) (noting that patent law offers "potential financial reward as an inducement to invent" and "to disclose technical information").

[112] *See* Michael Abramowicz, *The Danger of Underdeveloped Patent Prospects*, 92 CORNELL L. REV. 1065, 1073 (2007) [hereinafter Abramowicz, *Underdeveloped Patent Prospects*] ("[A] patent provides its holder a series of options . . . [such as] a development option to commercialize the invention."); *see also* Christopher A. Cotropia, *Describing Patents as Real Options*, 34 J. CORP. L. 1127, 1137 (2009) ("[The] exclusive use of the invention allows the patent holder to commercialize the invention and sell it at a supra-competitive price.").

[113] *See infra* Section III.B.

[114] *See infra* note 124 and accompanying text.

[115] For a recent study that found that the mean time between beginning clinical trials and market approval was 96.8 months (and 80.8 months from beginning clinical trials until

At the same time, doctrinal pressures in patent law require inventors to file their applications early.[116] This means that drugs aren't normally approved for marketing until long after the filing date of the underlying patent, shortening the "effective" term of the patent.[117] Partially for that reason,[118] Congress enacted the Hatch-Waxman Act to extend patent terms, recapturing time lost during the FDA's review.[119] At the end of the patent term, a generic manufacturer can file an Abbreviated New Drug Application (ANDA) to reach the market quickly, increasing competition and lowering drug prices.[120]

Although this framework works well for some novel drug development, it isn't as conducive to stimulating R&D into new uses for old drugs.[121] One reason is doctrinal. Patent law's doctrines

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submission of an NDA), see DiMasi et al., *Innovation in the Pharmaceutical Industry*, *supra* note 62, at 24. This did not include earlier stages of drug development, including preclinical research. *Id.* For earlier estimates, see, for example, Joseph A. DiMasi, *New Drug Development in the United States from 1963 to 1999*, 69 CLINICAL PHARMACOLOGY & THERAPEUTICS 286, 291 (2001).

[116] *See* Benjamin N. Roin, *Unpatentable Drugs and the Standards of Patentability*, 87 TEX. L. REV. 503, 518 (2009) (discussing the novelty doctrine); Rebecca S. Eisenberg, *The Role of the FDA in Innovation Policy*, 13 MICH. TELECOMM. & TECH. L. REV. 345, 351–52 (2007) (discussing novelty and statutory standards).

[117] *See, e.g.*, Henry G. Grabowski & John M. Vernon, *Effective Patent Life in Pharmaceuticals*, 19 INT'L J. TECH. MGMT. 98, 99 (2000) ("[E]ffective patent time is lost by pharmaceutical products because of the long period that a new drug spends in clinical trials and regulatory review.").

[118] *See, e.g.*, Gerald J. Mossinghoff, *Overview of the Hatch-Waxman Act and Its Impact on the Drug Development Process*, 54 FOOD & DRUG L.J. 187, 188 (1999) (detailing efforts by the Carter and Reagan Administrations to address pharmaceutical patents).

[119] *See* 35 U.S.C. § 156 (setting forth guidelines for extending a patent term).

[120] *See* IMS INST. FOR HEALTHCARE INFORMATICS, PRICE DECLINES AFTER BRANDED MEDICINES LOSE EXCLUSIVITY IN THE U.S. (2016) ("measur[ing] price declines following loss of exclusivity for every medicine that first became available as a generic between 2002 and 2014").

[121] Drug companies routinely file sNDAs for new indications, dosages, and patient populations. *See* DiMasi, *sNDAs*, *supra* note 28, at 818 (noting the increase in new-use approvals driven by new pediatric indications). But until recently, there was no data about whether these supplemental filings are made by drug companies with patents or market exclusivity over a use they are supplementing. *See* E-mail from Joseph DiMasi to David Simon (Oct. 27, 2020, 5:41 PM) (on file with author). A recent study found that new indications *exclusivities* are *never* added to the drug label after generics enter the market. *See* Babak Sahragardjoonegani, Reed F. Beall, Aaron S. Kesselheim & Aidan Hollis, *Repurposing Existing Drugs for New Uses: A Cohort Study of the Frequency of FDA-Granted New*

aren't equipped to protect all new uses.[122] Even if drug manufacturers do find and patent a new use, their reward is a method patent, which is difficult to enforce.[123] In some cases, manufacturers have successfully used new-use method patents covering an approved use of an existing off-patent drug to block

Indication Exclusivities Since 1997, 14 J. PHARM. POL'Y & PRAC. 1, 6 (2021). While this study adds important information, it does not examine all new indications, only those that received exclusivity. This information is critically important to understand just what effects patent law and drug regulation have on the quantity, quality, and type of sNDA applications. While the system may be working as intended, it is also possible that companies are using patent law and market exclusivities to extend their economic monopoly by filing sNDAs toward the end of the existing term of legal protection without conducting significant research. Data are simply not available to analyze these questions.

[122] The doctrines of novelty and nonobviousness present clear hurdles. *See* Abramowicz, *Underdeveloped Patent Prospects*, *supra* note 112, at 1100 (discussing issues with the nonobviousness doctrine); BTG Int'l Ltd. v. Teva Pharms. USA, Inc., 352 F. Supp. 3d 352, 387 (D.N.J. 2018), *appeal dismissed as moot*, BTG Int'l Ltd. v. Amneal Pharms. LLC, 923 F.3d 1063 (Fed. Cir. 2019) (finding obvious the combination of abiraterone acetate and prednisone to treat prostate cancer and reduce side effects); Acorda Therapeutics, Inc., v. Roxane Labs., Inc., 903 F.3d 1310, 1337 (Fed. Cir. 2018) (discussing the holding from Merck & Co. v. Teva Pharms. USA, Inc., 395 F.3d 1364 (Fed. Cir. 2005), and explaining that "the earlier patent and FDA regulatory approval [depress] incentives for others" to investigate new uses).

[123] *See* Timothy R. Holbrook, *Method Patent Exceptionalism*, 102 IOWA L. REV. 1001, 1014–18, 1033–34 (2017) (discussing the downsides of method patents and reviewing relevant court rulings). There are also public relations obstacles to enforcing method patents. *See* Sean B. Seymore, *Patenting New Uses for Old Inventions*, 73 VAND. L. REV. 479, 499–501 (2020) ("Method-of-use claims are difficult to enforce."); Eisenberg, *The Problem of New Uses*, *supra* note 25, at 724 ("[T]hese remedies are generally less satisfactory than an injunction that would stop a competitor from making the product entirely."); Rebecca S. Eisenberg, *The Role of the FDA in Innovation Policy*, 13 MICH. TELECOMM. & TECH. L. REV. 345, 351 (2007) [hereinafter Eisenberg, *Role of FDA*] (characterizing method patents as "less valuable").

generic entrants.[124] But until recently,[125] these suits usually required that the *approved labeling* read on a new use patent.[126]

[124] Companies also attempt to extend their monopolies by "product-hopping": patenting new formulations, such as extended release, of the same drug to extend their existing monopoly. *See* Dmitry Karshtedt, *The More Things Change: Improvement Patents, Drug Modifications, and the FDA*, 104 IOWA L. REV. 1129, 1134–36 (2019) [hereinafter Karshtedt, *Improvement Patents*] (detailing the reformulation of the drug Namenda to prevent generic entrants into the market); Michael D. Frakes & Melissa F. Wasserman, *Patent Office Reform and Drug Pricing* (forthcoming 2022) (manuscript at 4–5) (on file with author) (noting the extended period of exclusivity resulting from pharmaceutical patenting practices). To obtain product-hopping patents, drug companies will typically file a new NDA and use clinical trial data to support safety and efficacy findings. *See*, *e.g.*, CTR. FOR DRUG EVALUATION & RSCH., APPLICATION NUMBER 22-525: SUMMARY REVIEW (2010), https://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022525orig1s000sumr.pdf (stating that a single clinical trial had been performed for Namenda XR). The FDA also approved the drug subject to a small neurotoxicity study in female rats. Letter from Russell Katz, Director, Ctr. for Drug Evaluation & Rsch., U.S. Food & Drug Admin., to Michael Niebo, Forrest Labs., Inc. (June 21, 2010), https://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022525Orig1s000Approv.pdf. But because FDA approval is not comparative—because safety and efficacy are measured against a placebo and another drug—the "new" drug may be clinically identical to the pioneer. *See* Karshtedt, *Improvement Patents*, *supra* note 124, at 1140 ("The agency typically does not ask the sponsor to furnish any data suggestive of clinical distinctiveness between a drug's new form and its previous one . . . ."); Barbara J. Evans, *Seven Pillars of a New Evidentiary Paradigm: The Food, Drug, and Cosmetic Act Enters the Genomic Era*, 85 NOTRE DAME L. REV. 419, 491 (2010) (noting that comparative study data rarely exist); Theodore W. Ruger, *After the FDA: A Twentieth-Century Agency in a Postmodern World*, *in* FDA IN THE 21ST CENTURY 80–83 (Holly Fernandez Lynch & I. Glenn Cohen eds., 2015) ("FDA has codified by longstanding regulation a policy of assessing efficacy against placebo controls.").

[125] Glaxosmithkline LLC v. Teva Pharms. USA, Inc., 976 F.3d 1347, 1356 (Fed. Cir. 2020), *rehearing granted, opinion withdrawn* (Feb. 9, 2021), *on rehearing*, 7 F.4th 1320 (Fed. Cir. 2021) (upholding a jury verdict of induced infringement of a method patent where the jury found that promotion of the generic version of a brand name drug could infringe the method patent covering the use of brand name drug where the generic drug manufacturer knows its drug will be substituted for the brand name drug).

[126] *See, e.g.*, AstraZeneca LP v. Apotex, Inc., 633 F.3d 1042, 1058–61 (Fed. Cir. 2010) (holding that recommended "downward titration" language on the label of an ANDA could induce users to infringe a method patent covering a one-per-day use of the underlying drug because *some* patients using the generic would, according to the label, *necessarily* have to use the product once-per-day when titrating down to the lowest effective dose); Sanofi v. Watson Labs. Inc., 875 F.3d 636, 645–646 (Fed. Cir. 2017) ("The content of the label in this case permits the inference of specific intent to encourage the infringing use."); Vanda Pharm. Inc. v. W.-Ward Pharm. Int'l Ltd., 887 F.3d 1117, 1130 (Fed. Cir. 2018), *cert. denied sub nom*. Hikma Pharm. USA Inc. v. Vanda Pharm. Inc., 140 S. Ct. 911 (2020) (affirming the district court's finding of induced infringement). *But see* Bayer Schering Pharma AG v. Lupin, Ltd., 676 F.3d 1316, 1321–25 (Fed. Cir. 2012) (reaffirming *Warner-Lambert* and finding no grounds

Whenever that doesn't happen—when the generic label simply includes the off-patent use or doesn't specifically require practicing the new method[127]—it's difficult, though now potentially easier than in the past,[128] to enforce a new use patent.[129] So once the patent protection of an existing drug lapses, generics can usually enter the market by filing an ANDA. And once the generic enters the market, doctors can prescribe the drug for *any approved or unapproved use*, including patented new uses.

With only a modest threat of inducement actions, generics can potentially free-ride on the innovative use.[130] And there is very little

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for inducement based on the labeling of the drug, where the allegedly infringing labeling occurred in the "pharmacodynamics" subsection of the "Clinical Pharmacology" label and federal regulations expressly provided that such sections did not indicate approved uses); Erika Lietzan, *Paper Promises for Drug Innovation*, 26 GEO. MASON L. REV. 168, 194–95 ("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."). It is possible to imagine contributory infringement for *advertising* off-label, on-patent uses. But this situation doesn't arise frequently because of limits on off-label advertising. Simon, *Off-Label Information*, *supra* note 67, at 7–9.

[127] This practice of "carving out" the infringing use, also known as "skinny-labeling," is permitted by law. *See* 21 U.S.C. § 355(j)(2)(A)(viii) (allowing inclusion of "a statement that the method of use patent does not claim" a use for which the applicant is seeking approval); *see also* 21 C.F.R. § 314.94(a)(8)(iv) (2020) (detailing rules for comparing proposed and approved labeling for ANDAs).

[128] A Federal Circuit panel recently reheard a case in which it affirmed a jury's finding of infringement under a seemingly looser evidentiary standard. *See* Glaxosmithkline LLC v. Teva Pharms. USA, Inc., 7 F.4th 1320, 1340 (Fed. Cir. 2021) ("It was fair for the jury to infer that when Teva distributed and marketed a product with labels encouraging an infringing use, it actually induced doctors to infringe.").

[129] *See, e.g.*, Warner-Lambert Co. v. Apotex Corp., 316 F.3d 1348, 1362 (Fed. Cir. 2003) ("Because Apotex is not submitting an application to sell a drug for . . . the only use covered by the patent involved in this case, . . . Apotex is entitled to summary judgment . . . ."); AstraZeneca Pharms. LP v. Apotex Corp., 669 F.3d 1370, 1380 (Fed. Cir. 2012) (finding noninfringement based on the same reasoning in *Warner-Lambert*); Allergan, Inc. v. Alcon Lab'ys, Inc., 324 F.3d 1322, 1324 (Fed. Cir. 2003) (basing a finding of noninfringement on *Warner-Lambert*); *Bayer Schering Pharma*, 676 F.3d at 1326 (finding noninfringement based on the same reasoning in *Warner-Lambert* and *Allergan*).

[130] *See Underdeveloped Patent Prospects*, *supra* note 112, at 1069–70 ("With the patent in the public domain, any private party desiring to perform such scientific testing must also consider the possibility that third parties will free ride on the information its tests produce."). The free-riding problem is not as much of a concern when a drug is brought to market under an existing patent term because the patentee will have incentives, if not to develop, then at least to market as many novel uses as possible. *See id.* at 1102–03. This is a feature of drug regulation that is often seen as a problem, rather than a benefit. *Id.* at 1070. But the free-

pioneer drug companies can do about it.[131] State laws requiring generic substitution and insurance reimbursement rules[132] also reduce firms' incentives to invest in R&D of new uses for approved drugs whose patents have expired.[133] If firms can't exclude generics from market entry through an off-patent drug with an on-patent indication *and* doctors are free to prescribe drugs off-label, then a pioneer will have no ability to charge supra-competitive prices. Some new uses, in other words, will go undeveloped.

2. Market & Data Exclusivity. Patent law, it turns out, isn't currently incentivizing firms to adequately invest in unapproved new uses of approved drugs. For some of the same reasons, patent law is particularly bad at incentivizing other drugs, such as those for rare diseases where the market is often too small to risk drug development.[134] To provide an incentive in cases where patent law

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riding problem will exist as to post-patent and drug exclusivity terms for off-label uses. The problem here is that no one has sufficient incentive to invest in persuasion (clinical trials) because current prescribing practices enable generics to be used for off-label uses.

[131] *See infra* notes 144–147 and accompanying text.

[132] States began enacting these laws in the 1970s. *See* Henry G. Grabowski & John M. Vernon, *Substitution Laws and Innovation in the Pharmaceutical Industry*, 43 L. & CONTEMP. PROBS. 43, 49 (1979). Substitution laws, which all states have, take two forms. *See* New York *ex rel.* Schneiderman v. Actavis PLC, 787 F.3d 638, 644–45 (2d Cir. 2015). "[T]he first type of law specifies whether it is mandatory or permissive for a pharmacist to substitute a generic bioequivalent. The second type of law regulates whether the pharmacist should assume the patient's consent for generic substitution, or if they must explicitly request consent." Yan Song & Douglas Barthold, *The Effects of State-Level Pharmacist Regulations on Generic Substitution of Prescription Drugs*, 27 HEALTH ECON. 1717, 1718 (2018). States may have either or both kinds of laws. *See id.* For more detailed rules about when and what drugs can be substituted by whom, see generally Jesse C. Vivian, *Generic-Substitution Laws*, 33 U.S. PHARMACIST 30 (2008). Importantly, as well, some states prevent insurers from refusing to reimburse off-label uses. *See, e.g.*, Richardson v. Miller, 44 S.W.3d 1, 14 (Tenn. Ct. App. 2000) (describing Tennessee's statute prohibiting insurers from declining to pay for off-label uses); *see also* James M. Beck & Elizabeth D. Azari, *FDA, Off-Label Use, and Informed Consent: Debunking Myths and Misconception*s, 53 FOOD & DRUG L.J. 71, 76–77 & n.56 (1998) (discussing the policy guiding New Jersey's statute requiring insurers to pay for off-label uses).

[133] *See* Roin, *supra* note 26, at 33–35 (outlining how generic drugs can enter markets and reduce pharmaceutical investments with off-patent indications); *see also Warner-Lambert*, 316 F.3d at 1359 (rejecting plaintiff's claim that indication-based exclusivity undercut its market).

[134] *See* David Duffield Rohde, *The Orphan Drug Act: An Engine of Innovation? At What Cost?*, 55 FOOD & DRUG L.J. 125, 126–27 (2000) ("[R]are diseases, with their small patient

fails, Congress created various periods of regulatory "exclusivity"—periods in which the FDA will not approve the same drug for the same indication or will not allow competitors to use the successful applicant's data for its own application—for firms that develop and seek approval of various drugs.[135] Examples of some exclusivity periods include seven years of market exclusivity for drugs treating rare diseases,[136] five years of data exclusivity for new chemical entities (NCEs),[137] three years of data exclusivity for new uses of existing drugs,[138] and 180 days of market exclusivity for the first generic filer of an existing drug.[139] This incentive is particularly powerful for NCEs because the FDA will not approve any other drug with the same active ingredient during the statutorily defined period.[140] With the market to itself, a drug company can recoup investment costs and extract rents. Market exclusivity, in this way, provides an incentive for drug development where patent law can't or won't.

Although regulatory exclusivity is expressly designed to incentivize R&D of new uses, it's dysfunctional for two different reasons. First, just as with orphan drugs, it's often irrational to pursue new uses—even with the prospect of three-year data exclusivity—because there are better margins elsewhere.[141] Firms pursuing new uses may find smaller patient populations, less serious diseases, and little patent protection. Although "back-end" regulatory exclusivity helps mitigate the lack of patent protection,

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populations, provided little or no economic incentive . . . to invest research dollars in search of a cure whose development costs could not be recouped.").

[135] *See* Roin, *supra* note 26, at 10. I also refer to uses protected by market exclusivities as "protected uses." The EU has a similar approach for market and data exclusivity, but it functions somewhat differently, though with similar null effect, for new uses of approved drugs. *See* Liddicoat et al., *supra* note 103, at 826–27, 843.

[136] The Orphan Drug Act of 1983, 21 U.S.C. § 360cc; 21 C.F.R. § 316.31 (2020). In 1997, Congress sought to encourage clinical trials in pediatric populations by providing a six-month patent term extension or market exclusivity to firms that successfully completed such studies. 21 U.S.C. §§ 355a(b)(1), (c)(1), 355c.

[137] 21 U.S.C. § 355(c)(3)(E)(ii).

[138] 21 U.S.C. § 355(c)(3)(E)(iii).

[139] 21 U.S.C. § 355(j)(5)(B)(v).

[140] 21 C.F.R. § 314.108(b)(2) (2020).

[141] *See* Rohde, *supra* note 134, at 125–28 (describing the rationale for market exclusivity for orphan drugs).

it is often not enough to induce firms to invest in new uses.[142] Firms are better off investing in drugs that have a wider consumer base and a longer exclusivity period. Novel drug development, despite its increased risks, pays much higher returns.[143]

Second, regulatory exclusivity, like ANDA approval, is indication specific.[144] A generic can file an ANDA for any approved use not covered by a regulatory exclusivity.[145] If the FDA approves that ANDA, physicians can and will prescribe the drug for the protected use.[146] Because the FDA doesn't prevent physicians from prescribing the generic drug for protected uses, the generic use can

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[142] *See* Rohde, *supra* note 134, at 126 (detailing how the pharmaceutical industry "was concerned more with making profits through rational business decisions" and, because new drugs are more profitable and incentivized than new uses, the industry focuses R&D on new drugs and therapies).

[143] Perhaps even more profitable is extending the exclusivity of an existing drug through various legal and market-based machinations. *See* Karshtedt, *Improvement Patents*, *supra* note 124, at 1209–10 (contending that "there are reasons to believe that new use inventions are under-incentivized under the current regime").

[144] *See* Bristol-Myers Squibb Co. v. Shalala, 91 F.3d 1493, 1500 (D.C. Cir. 1996) (finding that the pioneer drug manufacturer is only granted three-year exclusivity for new *indications* that it adds to the label itself and not for new *indications* added by other manufacturers); Sigma-Tau Pharms., Inc. v. Schwetz, 288 F.3d 141, 146 (4th Cir. 2002) (finding that the agency's provision concerning exclusivity "of the same drug product for the same *indication*" was reasonable under the Food, Drug, and Cosmetic Act (emphasis added)). The difference, however, is that new uses can theoretically be enforced, while market exclusivities provide for no private enforcement mechanism. *See infra* Part III; Erika Lietzan, *Paper Promises for Drug Innovation*, 26 GEO. MASON L. REV. 168, 207 (2018) (arguing that Benjamin Roin's proposal isn't workable because it requires private enforcement of market exclusivity). *But see* Sam F. Halabi, *The Drug Repurposing Ecosystem: Intellectual Property Incentives, Market Exclusivity, and the Future of "New" Medicines*, 20 YALE J.L. & TECH. 1, 28–29 (2018) (noting that a price increase of an existing drug after market exclusivity was granted for new orphan indications). For orphan drugs there is another risk: a competitor drug can enter the market because it is "clinically superior." 21 C.F.R. § 316.3(b)(14)(i)–(ii) (2020) (creating an exception in the definition of "same drug" that "if the subsequent drug can be show to be clinically superior to the first drug, it will not be considered the same drug"); Berlex Lab'ys, Inc. v. Food & Drug Admin., 942 F. Supp. 19, 27 (D.D.C. 1996) (affirming FDA's approval of a competitor product under the Orphan Drug Act based on its clinical superiority).

[145] This is true even if the generic changes the proposed dosage to better match the use still subject to market exclusivity. *See* Spectrum Pharms., Inc. v. Burwell, 824 F.3d 1062, 1066, 1067–68 (D.C. Cir. 2016).

[146] The generic label must "carve out" any references to drugs currently under market exclusivity. 21 C.F.R. § 314.94(a)(8)(iv) (2020). This results in a "skinny label."

erode the profits gained through regulatory exclusivity.[147] This fact, combined with mandatory state substitution laws, effectively destroys the pioneer's exclusivity. So the promise of regulatory exclusivity often doesn't incentivize the research and development of new uses.

3. The Problem of New Uses as an Informational Problem. In short, neither market exclusivities nor new-use patents will block a generic from entering the market. Once the generic breaks into the market, the pioneer has little incentive to seek FDA approval for a new use because any such approval won't provide market exclusivity, or at least not any meaningful form of it. But even where a new use is both patented and approved by the FDA, in most cases the generic can avoid infringement by filing an ANDA for only non-infringing or unprotected uses. Firms, therefore, will be reluctant to expend resources to develop new uses—either by filing new-use patents or seeking market exclusivities for new uses.[148] This, in a nutshell, is the Problem of New Uses: how can the law incentivize the discovery of new unapproved uses when patent law and drug regulation can't protect the inventor from free-riding?

This problem, in turn, is about the appropriate incentives necessary to generate two kinds of information: information about *possible* new use candidates and safety and efficacy information about *identified* new uses.[149] Most of the existing proposals tacitly assume that these questions can be answered together, so their solutions assume that fixing market incentives for pharmaceutical companies will solve both informational Problems. One group of

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[147] *See Spectrum Pharms.*, 824 F.3d at 1066, 1068 (holding plausible the FDA's interpretation of 21 C.F.R. § 316.3(b)(12), (14), which explains that the exclusivity periods apply to the "same drug for the same use or indication" and states that "*[s]ame drug* means: . . . 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," to allow carve outs and varied generic dosages resulting in ANDA approval).

[148] To the extent it generates new use patents *despite this* is a curious phenomenon. If the patentee can't recoup costs or extract rents, then the patentee has effectively wasted her money. At the same time, this creates a positive spillover, one that simultaneously achieves and undermines the entire purpose of patent law: it excludes from the world a method that all physicians and patients are free to use. *But see* Karshtedt, *Improvement Patents*, at 1178–91 (arguing that by "product hopping" pharmaceutical companies extend patents to maintain market power once the primary patent protection expires without adequate evidence that supports a switch).

[149] This distinction is explained in more detail *infra* Section II.C.

scholars thinks the real problem is not with the laws but with their enforcement. Patent law and market exclusivities, in other words, could prevent free-riding, but only if they are enforced differently. Erika Lietzan, for one, argues that the solution is to bolster the doctrine of contributory infringement and FDA rules to enable better enforcement.[150] Benjamin Roin, on the other hand, thinks that better enforcement is a matter of better information.[151] Currently drug companies don't have access to information about when physicians are prescribing drugs off-label. If they did, drug companies could enforce their new-use patents. In other words, what's problematic about new uses is not a gap in the patent or drug laws, but one in information.

New uses, it's true, can be found by drug companies. But they can be—and often are—found by other actors, like physicians.[152] More recent work by Sam Halabi on the secondary use market has shown that enforcement-centered proposals miss a substantial part of innovative activity and are, therefore, unlikely to solve the Problem of New Uses entirely.[153] Halabi's research shows that repurposing occurs through a variety of direct and indirect mechanisms, including off-label marketing, serendipity, directed research, and private-academic partnerships.[154] Crucially, however, this scholarship—whether focused on the enforcement of traditional legal tools or the alternative ecosystem for new uses—doesn't directly tie the Problem of New Uses to the one of Off-Label Uses.

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[150] Lietzan, *Paper Promises*, *supra* note 144, at 195–204, 208–09 (detailing the difficulty in pursuing private action against generic drug companies and contending that "[t]he problem is not that the patent and regulatory exclusivity statutes are poorly drafted" then explaining how to strengthen federal law and contributory infringement as potential solutions to infringement).

[151] *See* Roin, *supra* note 26, at 59–60 (addressing different strategies to solve the problems raised herein but ultimately focusing on the use of informational technology, such as tracking de-identified patient prescribing and medical records, to enforce new-use patents).

[152] *See* Halabi, *supra* note 144, at 30 (listing academic researchers, clinicians, and pharmaceutical firm researchers as drivers of new drug indications). Halabi also notes, importantly, that firms reached for patent law by moving one step backwards in the chain of drug development: patenting *the method of finding new uses* itself. *See id.* at 37.

[153] *See id.* (discussing the secondary use market as a source of patent activity).

[154] *See id.* at 30, 32, 36 (describing serendipitous discovery, big data and in silico screening, and industry-university partnerships).

C. THE COMMON INFORMATIONAL OVERLAP

While the Problems of New Uses and Off-Label Uses seem different, they are actually the same problem. The information needed to *validate* a new use—to determine whether it is safe and effective for a given use—is the same information needed to validate an off-label use. That's because *any* new use of an approved drug is an off-label use. In other words, safety and efficacy information about new uses is also safety and efficacy information about off-label uses.

The converse is also sometimes true. Off-label uses may turn out to be new. Validating these off-label uses, then, will also validate the new uses. *Identifying* a new use, however, is a task that can occur only for uses that are new.[155] And this excludes a large portion of drugs prescribed off-label. To put things another way, the Problem of New Uses is concerned with *both* identification and validation; the Problem of Off-Label Uses is concerned only with validation. The fact that both Problems are about substantially the same information suggests that a single informational remedy could solve both Problems.[156]

Despite this fact, most solutions to either Problem tend to ignore it. Because scholars view each problem as distinct, their solutions tend to focus on entities that are unlikely to be able to solve them. For off-label uses, this means increasing government regulation to limit the practice. Predictably, most scholarship in this camp emphasizes the drawbacks of off-label prescribing rather than its

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[155] Just how "new" an off-label use must be for it to be considered "new" is a matter of definitional hair splitting. The National Center for Advancing Translation Sciences (NCATS) Discovering New Therapeutic Uses for Existing Molecules program (New Therapeutic Uses Program), for example, attempts to "accelerate the pace at which discoveries are turned into new preventions, treatments and cures for human diseases." *About New Therapeutic Uses*, NAT'L CTR. FOR ADVANCING TRANSLATION SCIS., https://ncats.nih.gov/ntu/about (last visited Mar. 3, 2022). The program is principally focused on *repurposing* drugs for *undiscovered* or *unidentified* new uses, not researching and developing existing off-label uses with insufficient safety and efficacy data. *See id.* But "new uses" might simply refer to existing off-label uses without sufficient safety and efficacy information.

[156] Some subsets of new uses are not problems to be solved but rather are solved problems. Currently firms *do* file sNDAs over some new uses. *See infra* Part III. For these approved new uses, existing incentive structures *seem* to be working to both identify and generate R&D for the new uses. *See infra* Part III.

innovative potential.[157] Besides squelching potentially innovative activity, discouraging off-label use also has another unintended consequence: it decreases the total amount of information about the incidence, nature, and effects of off-label use. This poses a real problem for any solution that seeks more information about off-label uses.

New uses, on the other hand, are seen as a problem for pharmaceutical companies to solve. All they need are the right incentives. Unfortunately, scholars have yet to identify them. But even if they could find proper incentives, both Problems would still remain. That's because increased R&D of new uses by pharmaceutical companies won't necessarily lead to more *public knowledge* of either identification or validation of new uses—or even to a large number of developed new uses. For one thing, there are simply too many potential new uses to investigate. For another, not all new uses, even if developed, will be profitable. Additionally, competition concerns may drive large firms to keep new uses secret. More than that, however, a firm-based solution ignores the fact that physicians, not just firms, identify and prescribe many new uses.[158] It also overlooks the large caches of information about off-label uses generated by other parties, such as payers and, as argued in the next Part, providers.

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[157] *See* Rodwin, *supra* note 78, at 654–55 (discussing the drawbacks of off-label prescriptions, including undermining the FDA's mission to regulate the drug market and protect patients).

[158] The problem here is that physicians don't communicate their innovations because there are limited incentives for them to do so. Eric von Hippel, Harold DeMonaco & Jeroen P.J. de Jong, *Market Failure in the Diffusion of Clinician Developed Innovations: The Case of Off-Label Drug Discoveries*, 44 SCI. & PUB. POL'Y 121, 128 (2017). For a recent attempt to correct this market failure, see *supra* note 179. Legal obstacles to some effective modes of communication exacerbate this market failure in information diffusion. *See* Simon, *supra* note 67, at 14, 17 (explaining legal and practical challenges of the current FDA approach to off-label information dissemination); Christopher Robertson, *The Tip of the Iceberg: A First Amendment Right to Promote Drugs Off-Label*, 78 OHIO ST. L.J. 1019, 1022 (2017) (noting that the NDA and sNDA processes eliminate advertising for off-label uses, which means "physicians must rely on peer-reviewed articles and anecdotes from other physicians to learn about new [off-label] uses, rather than on company promotional efforts").

III. PROVIDERS AS A TOOL TO SOLVE THE PROBLEMS OF NEW AND OFF-LABEL USES

Solving both the Problems of Off-Label and New Uses requires recognizing that they are substantially the same informational problem. This Part proposes to fill the common informational hole by targeting the entities that are in a unique position to, or that already, collect data on, evaluate, research, or modulate off-label uses: providers—hospitals, healthcare networks, and even small physician practices. Not all providers, of course, are the same. Large academic medical centers may be more likely to conduct clinical trials than small physician-based practices. Insofar as providers have the capability to do any of these activities, they are not the only relevant entities. As others have pointed out, payers like insurance companies also have capabilities and pertinent information that could assist in generating the information needed for better drug regulation.[159]

But no one has yet made the case for providers. This Part does so. It explains why targeting providers is likely to produce actionable information that can mitigate or solve both Problems. Section A details provider infrastructure, such as electronic health records and digital prescribing systems, that can track prescriber and patient off-label activity. Sections B and C then show that providers have institutional features that make them ideal loci for information generation, analysis, and diffusion. This sometimes includes institutional infrastructure or organizational units that systematically track and monitor off-label uses (e.g., digital prescribing software and pharmacy and therapeutics committees), conduct clinical trials and observational studies (e.g., institutional review boards, trained and experienced personnel, and research support), and diffusion (e.g., marketing departments, research output, and know-how). Section D concludes by exploring how provider-based incentives dovetail with the FDA's new program

[159] *See, e.g.*, Eisenberg & Price, *supra* note 45, at 19 (calling notice to "demand side" innovation and remarking that payers may help curb unsafe and less effective off-label use because they have both an incentive to provide cheaper care and the access to some of the relevant information); Rachel E. Sachs, *Promoting Demand-Side Innovation: Prizes for Payers*, 4 J.L. & BIOSCIENCES 391, 391 (2017) (diving into the active role insurance companies may take in the innovation process).

(RWE Program), which is considering how it can use so-called "real-world evidence" "to help to support the approval of a new indication" for a previously-approved drug.[160]

A. DATA COLLECTION AND ELECTRONIC HEALTH RECORDS

Providers already have access to voluminous amounts of information about patients, including their prescriptions and diagnoses. Health care providers increasingly use digital information systems for at least some aspect of their practice. As part of the Electronic Health Records (EHR) Incentive Programs, explained below,[161] almost all hospitals,[162] and large percentages of other providers,[163] have adopted EHRs. Most providers now collect basic information about all of their patients in digitized form,

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[160] 21 U.S.C. § 355g. The FDA has already begun promoting the integration of clinical trials into practice settings. U.S. FOOD & DRUG ADMIN., FRAMEWORK FOR FDA'S REAL-WORLD EVIDENCE PROGRAM 10–11 (2018) [hereinafter FDA RWE FRAMEWORK], https://www.fda.gov/media/120060/download; Barbara J. Evans, *The Future of Prospective Medicine Under the Food and Drug Administration Amendments Act of 2007*, *in* Ruger, *supra* note 124, at 96–100 (detailing the evolution of processes that have been in place to collect real-world evidence).

[161] In April 2018, the CMS changed the program name from "EHR Incentive Programs" to "the Promoting Interoperability Programs." *Promoting Interoperability Programs,* CTRS. FOR MEDICARE & MEDICAID SERVS., https://www.cms.gov/Regulations-and-Guidance/Legislation/EHRIncentivePrograms (last visited Apr. 23, 2022). Related programs also exist. *E.g.*, ACT NETWORK, https://www.actnetwork.us/national (last visited Apr. 23, 2022) (explaining that the "ACT Network is a real-time platform allowing researchers to explore and validate feasibility for clinical studies" funded by the National Institutes of Health that seeks to share EHR among providers participating in clinical trials and currently claims to have over 150 million patient records).

[162] *See* Julia Adler-Milstein & Ashish K. Jha, *HITECH Act Drove Large Gains in Hospital Electronic Health Record Adoption*, 36 HEALTH AFFS. 1416, 1419, 1421 (2017) (exploring the large percentages of HER adoptions in hospitals); *see also 2018 Medicare Electronic Health Record (EHR) Incentive Program Payment Adjustment Fact Sheet for Hospitals*, CTRS. FOR MEDICARE & MEDICAID SERVS. (Oct. 10, 2017), https://www.cms.gov/newsroom/fact-sheets/2018-medicare-electronic-health-record-ehr-incentive-program-payment-adjustment-fact-sheet-hospitals ("We note that over 96% of eligible hospitals are meaningful users.").

[163] Chun-Ju Hsiao & Esther Hing, *Use and Characteristics of Electronic Health Record Systems Among Office-based Physician Practices: United States, 2001-2012*, 111 NAT'L CTR. HEALTH STAT. DATA BRIEF 1, 1–8 (2012), https://www.cdc.gov/nchs/data/databriefs/db111.pdf (showing that EHR increased among office-based physicians from 18.2% in 2001 to 71.8% in 2012).

including prescriptions, diagnoses, and patient histories.[164] Not only do providers already collect some of the needed information, but their use of EHRs also makes collecting additional information about off-label uses—and creating data fields for that new information—easier than developing a new (software) system from scratch. While new data collection and organization may increase demands on software and marginally increase short-term costs, data collection itself should be relatively simple with low fixed costs. Using existing EHR systems—and building them out—could also capture innovative off-label uses by, for example, allowing (or creating incentives for) physicians to flag uses that they think are new. Software systems could also capture various features of the new use that might enable researchers to identify the conditions under which new uses are likely to be discovered and, if discovered, when they are likely to be safe and effective.

B. INSTITUTIONAL BODIES AND EXPERTISE

All providers have the ability to collect certain kinds and quantities of information about off-label use. Many, as noted above, could leverage this capacity to collect information about off-label and new uses that they initiate simply by practicing medicine. Large providers, in particular, have the ability to collect more data and in a more systematic and nuanced way than smaller providers. Some, in fact, already have an institutional body designed to collect and analyze information about drug prescriptions, use, and effects: the Pharmacy and Therapeutics committee (P&T committee).[165]

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[164] *See, e.g.*, 42 C.F.R. §§ 495.20(d)(1)(i) (2020) (computerized provider order entry), (d)(2) (drug interactions and allergy checks), (d)(3) (diagnosis information), (d)(4) (e-prescribing), (d)(5) (indication tracking), (d)(6) (medication allergy list), (d)(7) (demographics), (d)(8) (vital signs), (d)(9) (smoking status), (d)(10) (clinical quality measurements), (d)(11) (tracking clinical compliance), (d)(12) (patient record copies), (d)(13) (patient clinical summaries), (d)(14) (information exchange), (d)(15) (privacy protections).

[165] Hospitals first established P&T committees in 1936. *See* Robin Feldman, *The Devil Is in the Tiers*, 8 J.L. & BIOSCIENCES 1, 7–8 & n.30 (2021). They became requirements for Joint Commission accreditation in 1965. *Id.* The Joint Commission accredits hospitals both independently and for Medicare and Medicaid. *See infra* notes 166, 168, 244.

A hospital's P&T committee develops a "formulary" of drugs that the provider uses to determine which drugs to dispense.[166] The formulary represents the judgment of the institution's medical staff about the safety and efficacy of various drugs.[167] The P&T committee also evaluates and monitors the use of medications; collects information about adverse events, reporting, and medication errors; and develops "clinical care plans" and guidelines.[168] At more sophisticated providers, the P&T committee is the primary liaison between the pharmacy and the medical staff.[169] Various subcommittees report and make recommendations

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[166] *See* David Shulkin, *Reinventing the Pharmacy and Therapeutics Committee*, 37 P&T 623, 623 (2012) ("[T]he P&T committee has the overarching goal of ensuring the safe, appropriate, and cost-effective use of pharmaceuticals."). In 2008, the influential American Society of Health-System Pharmacists (ASHP) published guidelines for institutions seeking to establish a formulary and P&T system. *See* Christy Ciccarello et al., *ASHP Guidelines on the Pharmacy and Therapeutics Committee and the Formulary System*, 78 AM. J. HEALTH-SYS. PHARM. 907, 915 (2021) [Ciccarello, *ASHP Guidelines*]. It also offers accreditation for those that conform to its guidelines. *See id.* at 907. This accreditation, however, is not an approved Medicare accreditation under 42 U.S.C. § 1395bb or 42 C.F.R. § 482 *et seq*. *See id.* at 907, 913. For an in-depth review on how the formulary system works at a large medical center, see David B. Nash, Mary L. Catalano & Cindy J. Wordell, *The Formulary Decision-Making Process in a US Academic Medical Centre:*, 3 PHARMACOECONOMICS 22, 22–35 (1993). There is considerable variation among hospitals both in the substantive content of formularies and the processes by which they manage them. *See* Ellena Anagnostis, Cindy Wordell, Yor Guharoy & Robert Beckett, *A National Survey on Hospital Formulary Management Processes*, 24 J. PHARM. PRAC. 409, 410–11 (2011). Anagnostis, Wordell, Guharoy, and Beckett, for example, found that although most institutions had written policies for how medications' additions to the formulary are requested and reviewed, they had far fewer policies for formulary deletion. *See id.* at 411*; see also* Gordon D. Schiff et al., *Drug Formulary Decision-Making: Ethnographic Study of 3 Pharmacy and Therapeutics Committees*, 76 AM. J. HEALTH-SYS. PHARM. 537 (2019) (noting that findings showed "wide variations" in "discussions of new drug formulary requests").

[167] *See* Nash et al., *supra* note 166, at 23 ("[T]he medical staff of an institution, working through the pharmacy and therapeutics committee, evaluates, appraises, and selects . . . those [drugs] that are considered most useful to patient care.").

[168] Ciccarello, *ASHP Guidelines*, *supra* note 166, at 908; *see also* Nash et al., *supra* note 166 at 23, 25 (explaining the structure and function of P&T committees); Darryl S. Rich, *Pharmacies' Noncompliance with 2009 Joint Commission Hospital Accreditation Requirements*, 67 AM. J. HEALTH-SYS. PHARM. 144, 144–45 (2010) (explaining the various ways in which P&T committees may add a drug to the formulary either because of an FDA-approved labeling or because the P&T committee has determined it should be added).

[169] Nash et al., *supra* note 166, at 25.

to the P&T committee, which then makes recommendations to the medical staff and administration of the provider.[170]

Some providers, in other words, have a built-in infrastructure to generate, collect, monitor, analyze, and operationalize information about off-label uses[171]—and to do so at a level of granularity not normally available elsewhere. At one provider, the P&T committee will do all of the following in a ten-month cycle: "evaluate 45 new drugs for formulary addition, review 3 therapeutic classes of drugs, discuss 150 adverse events, . . . review 10 drug use evaluations," and "review[] the medical staff policies regarding the prescribing and dispensing of medications in the institution."[172] Put differently, P&T committees are a significant source of information about off-label use that is currently underutilized.[173]

P&T committees not only have expertise in evaluating drugs, but they also have unique information about innovative new uses. Physicians may request a new addition to the formulary—and that new addition may be an innovative off-label use. While not all innovative new uses will take place at providers with P&T committees, they all will take place at *a* provider. Regardless of whether the physician works in a hospital with a P&T committee or a small practice, she has limited incentives to both collect information about and disseminate any discovered new use.

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[170] *Id.* at 24–25.

[171] This framework has been used to evaluate pre-1938 drugs that the FDA wants to test for efficacy and safety. Colleen M. Culley, Beth Ann Carroll & Susan J. Skledar, *Formulary Decisions for Pre-1938 Medications*, 65 AM. J. HEALTH-SYS. PHARM. 1363, 1364–66 (2008). When Congress passed the 1962 Kefauver-Harris Amendments, it grandfathered in drugs that had been sold prior to 1938. CTR. FOR DRUG EVALUATION & RSCH., U.S. DEP'T OF HEALTH & HUM. SERVS., GUIDANCE FOR STAFF AND INDUSTRY: MARKETED UNAPPROVED DRUGS COMPLIANCE POLICY GUIDE, SEC. 440.100,11 (2011). The FDA evaluated drugs approved between 1938 and 1962 in its Prescription Drug Wrap-Up. *Id.* at 11.

[172] Nash et al., *supra* note 166, at 25.

[173] Federal regulations also require Medicare Part D sponsors that use formularies (graded pricing mechanisms) to create a P&T committee develop and implement them. 42 C.F.R § 423.120(b) (2020). All Part D sponsors use formularies to decide which drugs to reimburse. Although, theoretically, this process is designed to reduce drug spending, it has, in practice, led to significant price distortions and increases. *See, e.g.*, ROBIN FELDMAN, DRUGS, MONEY, & SECRET HANDSHAKES: THE UNSTOPPABLE GROWTH OF PRESCRIPTION DRUG PRICES 39–42 (2019) ("Medicare health insurance plans may create incentives in certain circumstances for higher drug prices.").

While P&T committees may have information but lack incentives to disseminate it, the providers where they're located typically have other infrastructure that could do so rather efficiently.[174] Academic medical centers and hospitals, for example, have institutional resources allocated to marketing, publication, and dissemination of various kinds of information (e.g., research, promotional material). Some also have students, graduate students, administrative staff, compliance departments, and marketing officers. All of these institutional resources make academic medical centers and (larger) hospitals well placed to disseminate whatever information they collect and analyze. Large healthcare networks with smaller embedded healthcare practices—like NorthShore University HealthSystem,[175] Mass General Brigham,[176] and Health Partners[177]—have similar advantages.

Small providers, which constitute almost half of all medical practices, face different challenges.[178] They are, for example, less

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[174] The growing body of medical networks—such as Partners Healthcare (Massachusetts), Northshore (Illinois), and Health Partners (Minnesota)—impose P&T requirements on providers in their networks. *See infra* notes 175–177. As consolidation in HealthCare services increases, so does the potential for standardizing these collection, organization, and analysis of off-label use.

[175] This includes five hospitals in the Chicagoland area, including a "900 physician multispecialty group practice." *Organizational Profile*, NORTHSHORE UNIV. HEALTHSYSTEM, northshore.org/about-us/organizational-profile/ (last visited Apr. 23, 2022).

[176] Until 2019, this entity was known as Partners Healthcare. *See Our* Story, MASS GENERAL BRIGHAM, https://www.massgeneralbrigham.org/who-we-are/our-story (last visited Apr. 23, 2022). The organization includes "16 member institutions that encompass a range of health care organizations. In addition to our academic medical centers, these include top-tier specialty hospitals, community hospitals, a rehabilitation network, a health insurance plan, a physician network, a teaching organization, and many locations for urgent and community care." *Id.*

[177] HealthPartners is "the largest consumer governed nonprofit health care organization in the nation – serving more than 1.8 million medical and dental health plan members nationwide. Our care system includes a multi-specialty group practice of more than 1,800 physicians that serves more than 1.2 million patients." *Our History*, HEALTHPARTNERS, https://www.healthpartners.com/about/ (last visited Apr. 23, 2022). HealthPartners also runs an "Institute" that conducts clinical research. *See Research*, HEALTHPARTNERS INST., https://www.healthpartners.com/institute/research/ (last visited Apr. 23, 2022).

[178] Carol K. Kane, *Updated Data on Physician Practice Arrangements: For the First Time, Fewer Physicians Are Owners than Employees*, AM. MED. ASS'N 5, 13 (2019) (noting that "[i]n 2018, 56.5 percent of physicians worked in practices with 10 or fewer physicians" while 14.7 percent worked in practices with fifty or more physicians and the remaining 20.3 percent working in practices between eleven and forty-nine physicians).

equipped to collect granulated data and disseminate it to the same extent as large providers. But they still may have valuable information about innovative off-label uses, and capturing this information, along with other off-label uses, is critical to solving both problems.

The FDA and the National Institutes of Health's National Center for Advancing Translational Sciences (NCATS) recently recognized this in the context of innovative off-label use and have launched a pilot program designed to correct the market failure in diffusion noted above.[179] While this recent initiative—which uses a decentralized, voluntary reporting model—is an interesting and positive development, it is designed to collect limited information about innovative off-label uses; without additional incentives, it is unlikely to solve both Problems.[180] And, as explained in Part III, any incentive structure that seeks to generate information about off-label uses must be responsive to provider characteristics.

C. INSTITUTIONAL KNOW-HOW AND EXPERIENCE

In addition to resources, providers also have institutional know-how. Many providers, for example, have experience conducting clinical trials and observational studies.[181] Sometimes providers themselves initiate these trials and fund them publicly; other times

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[179] This program, known as CURE ID, allows physicians anywhere in the world to report new uses to a government repository using a computer application. *CURE Drug Repurposing Collaboratory*, CRITICAL PATH INST., https://c-path.org/programs/cdrc/ (last visited Apr. 23, 2022). It is part of a larger project between the FDA and NCATS to aid in "repurposing and inform[ing] future clinical trials for diseases of high unmet medical need. The initiative includes emerging/reemerging diseases, anti-microbial drug resistant infections, neglected infectious diseases as well as rare oncology diseases where there are limited treatment options." *Id.* The drug is being pilot-studied with COVID-19. *Id.* Perusing the existing application shows that activity is minimal but has potential with greater practice-integration, data capture, and outreach. *Id.*

[180] Presently, the focus is on collecting and disseminating information on innovative uses of drugs to treat COVID-19.

[181] *See, e.g.*, Ruijun Chen et al., *Publication and Reporting of Clinical Trial Results: Cross Sectional Analysis Across Academic Medical Centers*, BMJ (Feb. 17, 2016), https://www.bmj.com/content/352/bmj.i637 (identifying 4,347 clinical trials at fifty-one academic medical centers in the United States from 2007 to 2010); *supra* note 177 (discussing HealthPartners Institute).

providers partner with private industry.[182] With greater incentives to gather safety and efficacy information about off-label uses, providers can capitalize on their existing knowledge base and skills and potentially expand their capacity. The benefits of doing this may extend beyond simply generating data: limited evidence suggests that providers who engage in clinical trials are likely to provide better care to non-trial patients.[183]

Despite the promise of both P&T committees and providers generally as a source of information about both off-label and new uses, there's little information about how providers collect and analyze information about off-label use, or if they do so at all. This is true despite the information reporting requirements on many providers.[184] The limited data that exist show that only a small number of providers have a policy in place to review off-label use, let alone analyze potentially beneficial new uses.[185] Providers that have policies lack incentives to share this information with outside providers or health care professionals.[186] One is a problem of generation, collection, and analysis. The other a problem of

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[182] Even smaller providers now have experience with clinical trials. *E.g.*, Sean R. Tunis, Daniel B. Stryer & Carolyn M. Clancy, *Practical Clinical Trials: Increasing the Value of Clinical Research for Decision Making in Clinical and Health Policy*, 290 JAMA 1624, 1627 (2003) (explaining that practical clinical trials take place in diverse clinical settings, which often include community-based clinics).

[183] *See* Sumit R. Majumdar et al., *Better Outcomes for Patients Treated at Hospitals That Participate in Clinical Trials*, 168 ARCHIVES INTERNAL MED. 657, 659 (2008).

[184] Besides its meaningful use criteria, *supra* note 162 and accompanying text, Medicare requires all of its certified institutional providers to "submit an annual cost report." *Cost Reports*, CTR. FOR MEDICARE & MEDICAID SERVS., https://www.cms.gov/Research-Statistics-Data-and-Systems/Downloadable-Public-Use-Files/Cost-Reports (last visited Apr. 23, 2022) (providing general cost report information and the cost reports of prior years); 42 C.F.R. § 413.20 (2020) (describing cost reports and their requirements).

[185] *See* Anagnostis et al., *supra* note 166, at 413 (noting variable formulary addition practices and that "(31%) of [the] 52 [responding] institutions[in the survey] have a policy and/or procedure for approving a medication for an off-label indication").

[186] *See*, *e.g.*, Kathleen Liddell, David A. Simon & Anneke Lucassen, *Patient Data Ownership: Who Owns Your Health?*, 8 J.L. & BIOSCIENCES 1, 47 (2021) (explaining that granting healthcare providers property rights over patients' data does not necessarily encourage sharing access to data across jurisdictions); Barbara J. Evans, *Much Ado About Data Ownership*, 25 HARV. J.L. & TECH. 69, 103–04 (2011) (discussing the high costs and many disadvantages of developing a centralized, national database containing individuals' complete medical history).

diffusion. Providers, while currently not meeting either of the challenges, could do so with the right incentives.

D. THE FDA'S REAL WORLD EVIDENCE PROGRAM

All of these features—use of EHRs, along with institutional expertise knowledge, know-how, and experience—make providers an important source of information about off-label use. But there is another reason for tapping the information they have about new and off-label uses: providers will be significant sources of "real world evidence" (RWE) that the FDA can rely upon to approve new uses of previously-approved drugs. Real world evidence is evidence derived from real world data (RWD): "clinical evidence regarding the usage and potential benefits or risks of a medical product derived from analysis of RWD."[187] RWE includes data from EHRs (including test results), claims, pragmatic trials, and observational studies.[188] The term became important in 2016, when Congress, as part of the 21st Century Cures Act, mandated that the FDA "establish a program to evaluate the potential use of real world evidence" to approve new indications[189] and to issue guidance to industry on the topic.[190]

While the FDA intends to use more RWE in approving new indications,[191] it has noted that the task is not without significant challenges, including data formatting, quality, and consistency (in capture).[192] As one example, the FDA notes that EHRs may not record patient symptoms, either in response to medication or at the conclusion of treatment, in a structured or standardized manner—

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[187] RWE Framework, *supra* note 160, at 29.

[188] *See* Liddell, *supra* note 186, at 6 (detailing how health information can be generated by a typical check-up); RWE FRAMEWORK, *supra* note 160, at 5, 11 (identifying examples of real world evidence).

[189] 21 U.S.C. § 355g(a).

[190] 21 U.S.C. § 355g(e)(1). In response to this congressional mandate, the FDA published its framework in 2018 and issued draft guidance in 2019. *See* RWE FRAMEWORK, *supra* note 160, at 3; U.S. FOOD & DRUG ADMIN., SUBMITTING DOCUMENTS USING REAL-WORLD DATA AND REAL-WORLD EVIDENCE TO FDA FOR DRUGS AND BIOLOGICS, DRAFT GUIDANCE (2019).

[191] *See* RWE FRAMEWORK, *supra* note 160, at 13.

[192] *See id.* at 15–17; Dr. Jacqueline Corrigan-Curay, *in* NCATS Meeting, *supra* note 30, at 60–61 (noting that validating clinical data is difficult because it may be collected sporadically or in many different forms, citing an example from the Sentinel Initiative where "there were 70 different ways to represent a single, very simple platelet count").

or at all.[193] Claims data, too, may exclude important metrics such as symptom severity and disease response.[194]

Many, but not all, of these problems result from the manner in which providers (or payers) collect information. Incentives that induce providers to generate off-label information can, as shown below, also be structured to mitigate or eliminate some of the challenges of using RWD and RWE.[195] Obtaining good information about off-label use, for example, requires some minimum amount of data in a uniform format. The same information is required to make assessments about the effects of off-label and new uses. Giving providers incentives to produce this information not only generates more useful, complete, and reliable information about off-label and new uses but also is a source of potential evidence that can be used to add a new indication to the drug label. This may be crucial if new approval pathways, such sua sponte FDA label changes or citizen petitions, are used. In sum, providers are capable of both generating information about new and off-label uses and compiling it in a format likely to qualify as RWD. What providers lack, however, are the incentives to do so. The next Part explains some of the potential incentive choices.

IV. INCENTIVES

This Part evaluates several potential incentives that could induce providers to capture and develop actionable data about off-label and new uses. The goal of this Part isn't to argue for any particular incentive or to show how every incentive might apply to providers. It is, instead, to show that incentives *can* induce providers to generate, collect, analyze, and disseminate information about off-label and new uses. For this reason—and because space is limited—this Part uses four examples to illustrate how provider incentives could work. One, described in Section B, is an existing government program designed to encourage providers to adopt EHRs. Section C then proposes a new incentive—market inclusivity—that would pay providers directly for implementing

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[193] *See* RWE FRAMEWORK, *supra* note 160, at 17.

[194] *See id.* at 17–18.

[195] *See id.* at 25 (discussing how the FDA will assess data standards and implementation strategies to ensure that RWD and RWE are central to drug development).

systems to track, organize, and publish data on off-label uses. Section D examines how a traditional push incentive, tax credits, could induce providers to engage in validation of off-label uses. Finally, Section E considers how altering the FDA approval process and regulatory exclusivity might further incentivize providers to conduct validation on off-label uses. Before exploring any of these incentives in detail, Section A explains the incentives traditionally used to stimulate pharmaceutical development.

A. INCENTIVES GENERALLY

Stimulating providers to collect, analyze, and disseminate information about off-label uses requires incentives. This, one will notice, is the same task typically performed by pharmaceutical companies. It is therefore reasonable to consider how the same suite of incentives used to stimulate pharmaceutical companies to engage in information generation can be applied to providers. These incentives fall into two categories. First, *push* or *ex ante* incentives are supply-side incentives that subsidize research: government

grants,[196] public-private partnerships,[197] and tax benefits.[198] Second, *pull* or *ex post* incentives are demand-side incentives that create a viable market for drug discovery: prizes,[199] patents, and regulatory exclusivity.[200]

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[196] The U.S. government funds clinical trials through various agencies, including the National Institutes of Health (NIH); National Heart, Lung, and Blood Institute (NHLBI); the Centers for Disease Control and Prevention (CDC); the FDA; and the CMS. *See* Robert M. Califf, Deborah A. Zarin, Judith M. Kramer, Rachel E. Sherman, Laura H. Aberle & Asba Tasneem, *Characteristics of Clinical Trials Registered in ClinicalTrials.gov, 2007–2010*, 307 JAMA 1838, 1841 tbl.1 (2012) (noting that the NIH funded around only 9% of all studies in ClinicalTrials.gov); Pearl A. McElfish, Rachel S. Purvis, M. Kathryn Stewart, Laura James, Karen H. Kim Yeary & Christopher R. Long, *Health Research Funding Agencies' Policies, Recommendations, and Tools for Dissemination*, 12 PROG. CMTY. HEALTH P'SHIP, 473, 475–78 (2018) (describing the funding policies of CDC, CMS, FDA, and NIH grants); David Gordon, Wendy Taddaei-Peters, Alice Mascette, Melissa Antman, Peter G. Kaufmann & Michael S. Lauer, *Publication of Trials Funded by the National Heart, Lung, and Blood Institute*, 369 NEW ENG. J. MED. 1926–34 (2013) (conducting "an extensive evaluation of the publication of the results of NHLBI-funded trials of cardiovascular interventions"); ORPHAN PRODUCTS CLINICAL TRIALS GRANTS PROGRAM, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/industry/about-orphan-products-grants (last visited Apr. 23, 2022) (describing the Orphan Products Clinical Trials Grants Program). The NIH currently funds some clinical trials for new uses of approved, off-patent drugs, but the Director of NCATS at the NIH notes that the "NIH does not like to pay for these." Dr. Christopher P. Austin, *in* NCATS Meeting, *supra* note 30, at 5.

[197] *See, e.g.*, *Templates for Success: Speeding the Formation of Public-Private Partnerships*, NAT'L CTR. FOR ADVANCING TRANSLATION SCIS., https://ncats.nih.gov/pubs/features/ntu-template (last visited Apr. 23, 2022); Rutger Daems, Edith Maes & Guy Nuyts, *Advancing Pharmaceutical R&D on Neglected Diseases: Valuing Push and Pull Economic Incentive Mechanisms* 10–12 (Maastricht Sch. Mgmt. Working Paper, No. 2013/11, 2013), http://web2.msm.nl/RePEc/msm/wpaper/MSM-WP2013-11.pdf; Henry Grabowski, *Increasing R&D Incentives for Neglected Diseases: Lessons from the Orphan Drug Act*, *in* INTERNATIONAL PUBLIC GOODS AND TRANSFER OF TECHNOLOGY UNDER A GLOBALIZED INTELLECTUAL PROPERTY REGIME 457, 463–64 (Keith E. Maskus & Jerome H. Reichman, eds. 2005).

[198] *See* 26 U.S.C. § 45C (laying out the orphan drug tax credit conditions); 26 U.S.C. § 41 (stating tax credits for research activities). For further discussion, see *infra* Section III.B.*3*.

[199] *See* WILLIAM W. FISHER, III & TALHA SYED, INFECTION: THE HEALTH CRISIS IN THE DEVELOPING WORLD AND WHAT WE SHOULD DO ABOUT IT ch.5 1 (Stanford University Press) (forthcoming), https://cyber.harvard.edu/people/tfisher/Infection_Prizes.pdf (explaining how a government prize system would incentivize pharmaceutical development and create a market); *see generally* James Love & Tim Hubbard, *The Big Idea: Prizes to Stimulate R&D for New Medicines*, 82 CHI.-KENT L. REV. 1519 (2007).

[200] Daems et al., *supra* note 197, at 12.

While the traditional method for generating new drugs has been dominated largely by patent law[201] and regulatory exclusivity,[202] it would be unwise to assume that the same mix of incentives—or the same incentives in exactly the same forms—will work for providers. Providers and drug companies have fundamentally different concerns, business models, and organizational structures. For incentives to be effective, they must be mindful of these differences.

Determining the optimal set, form, and breadth of provider incentives is beyond the scope of this Article. For that reason, the remainder of this Part doesn't attempt to explain the advantages and drawbacks of every possible incentive. Instead, it uses four examples to illustrate how incentives might induce providers to collect information that they already have or have the ability to produce. This information consists principally of either (1) existing data about the nature, incidence, and effect of off-label use or (2) data from observational studies and pragmatic or clinical trials. Some incentives, as shown below, can apply to both types of information, but they will have to be adjusted to ensure that they generate the right kind of information in each case.

B. BUILDING OUT EXISTING GOVERNMENT PROGRAMS

One way to incentivize providers to engage in a desired behavior is to pay them.[203] Congress used this strategy in 2009 to induce

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[201] *See, e.g.*, James Bessen & Michael J. Meurer, Patent Failure: How Judges, Bureaucrats, and Lawyers Put Innovators at Risk 16, 18 (2008) (describing how patent law creates incentives for pharmaceutical development).

[202] *See supra* note 200.

[203] There are other efforts to gather data, though. *See, e.g.*, *All-Payer Claims Databases*, AGENCY FOR HEALTHCARE RSCH. & QUALITY, https://www.ahrq.gov/data/apcd/index.html (last visited Apr. 23, 2022) (describing the project to update and improve state claims data from private insurance companies); Roxanne M. Andrews, *Statewide Hospital Discharge Data: Collection, Use, Limitations, and Improvements*, 50 HEALTH SERVS. RSCH. 1273, 1273–99 (2015) (describing Agency for Healthcare Research and Quality's (AHRQ) grants to states to update statewide discharge databases with race-ethnicity data); CTRS. FOR MEDICARE & MEDICAID SERVS., NATIONAL COVERAGE DETERMINATIONS WITH DATA COLLECTION AS A CONDITION OF COVERAGE: COVERAGE WITH EVIDENCE OF DEVELOPMENT § V.A (2006) (explaining that the CMS will provide coverage in some cases where there is "adequate evidence to determine that an item or service is reasonable and necessary" but that further evidence is needed that is not routinely available on claims forms); *id.* § V.B (explaining that CMS will cover items where there is insufficient evidence to determine an item is reasonable

providers to adopt EHRs,[204] awarding subsidies (push incentives) to providers,[205] states,[206] and Native American tribes.[207] Payment was conditioned on eligible providers adopting "meaningful uses" of EHR.[208] Meaningful uses was defined in detail, and the requirements were phased in through three stages over five years.[209] Providers that hit the CMS benchmarks obtained the subsidy;[210] those that failed to do so received nothing and, as of

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and necessary but where additional clinical data would aid in this determination, including requiring "added safety, patient protections, monitoring, and clinical expertise").

[204] This was included in the American Recovery and Reinvestment Act (ARRA) of 2009, part of which was the HITECH Act. *See* American Recovery and Reinvestment Act of 2009, Pub. L. No. 111-5, 123 Stat. 115 (2009) (codified as amended in scattered sections of 16 U.S.C. & 42 U.S.C.) (enacting an economic stimulus package in response to the Great Recession).

[205] *See, e.g.*, ARRA of 2009 § 4101(a) (codified at 42 U.S.C. 1395w-4(o)) (detailing meaningful use requirements and incentives); *id.* § 4101(b) (codified at 42 U.S.C. § 1395w–4(a)(7)) (detailing payment adjustments for physician services); *id.* § 4101(c) (codified at 42 U.S.C. § 1395w-23 (l)) (defining MA-affiliated eligible professionals); *id.* § 4102(a)(1) (codified 42 U.S.C. § 1395ww(n)) (detailing hospital incentives for use of certified CHR technology); *id.* § 4102(a)(2) (codified at 42 U.S.C. § 1395f(l)(3)) (describing payment requirements for inpatient hospital services).

[206] *See* HITECH Act § 3013 (codified at 42 U.S.C. 300jj–33). HITECH Act § 3014 (codified at 42 USC § 300jj–34) (describing grants to Native American tribes).

[207] HITECH Act § 3014 (codified at 42 USC § 300jj–34) (describing grants to Native American tribes).

[208] Eligible providers included physicians, Medicare advantage organizations, hospitals, critical access hospitals, MA organizations for certain affiliated hospitals, and states participating in Medicaid. 42 U.S.C. § 1395w–4(o) (SSA § 1848(o)) (defining eligible professionals); *id.* § 1395w–23(l) (SSA § 1853(1)) (detailing Medicare Advantage Organizations for certain affiliated professionals); *id.* § 1395ww(n) (SSA § 1886(n)) (defining eligible hospitals); *id.* § 1395f(l) (SSA § 1814(l)) (discussing payment to critical access hospitals); *id.* § 1395w–23(m) (SSA § 1853(m)) (detailing MA organizations for certain affiliated hospitals), 1396b(a)(3)(F), (t) (SSA 1903(a)(3)(F) & 1903(t)) (guiding states participating in Medicaid). Physicians, for example, were eligible for either the Medicare or Medicaid subsidy depending on whether they treated Medicare patients, or a certain volume of Medicaid patients. Eligible physicians could then elect to receive a subsidy under either program, but not both. *See* 42 U.S.C. § 1395w–4(k)(3) (defining eligible professional); Discussion on the Relationship Between a Stage 1 Meaningful Use Objective and Its Associated Measure, 75 Fed. Reg. 44,314, 44,437–38 (July 28, 2010) (noting initial election with one-time ability to switch elections); *id.* at 44,438 (noting that hospitals can choose between Medicare fee-for-service EHR incentive or the Medicare Advantage EHR incentive *and* the Medicaid EHR incentive).

[209] *See infra* note 205 (citing C.F.R.).

[210] *See, e.g.*, 42 U.S.C. § 1395ww(n)(3) (defining meaningful EHR user for hospitals and noting that the HHS secretary will set the standard). Implementation rules are located at 42

2015, were penalized.[211] Eligible hospitals,[212] for example, were entitled to a $2,000,000 base payment with additional payments determined by the number of patients discharged and a payment cap of $6,370,400.[213] Since 2015, providers that failed to meet the "meaningful use" requirements had their Medicare payments reduced.[214]

By the time the payments sunset in 2018,[215] the federal government had paid out around $25 billon under this program.[216]

C.F.R. § 495.20 (2020) (defining meaningful use objectives and measures for EPs, eligible hospitals, and critical access hospitals (CAHs) before 2015); 42 C.F.R. § 495.22 (defining meaningful use objectives and measures for EPs, eligible hospitals, and CAHs for 2015 through 2018); 42 C.F.R. § 495.24 (defining stage 3 meaningful use objectives and measures for EPs, eligible hospitals and CAHs for 2019 and subsequent years).

[211] 42 U.S.C. §§ 1395w–4(a)(7), 1395w–23(l)(4),1395ww(b)(3)(B)(ix)(I), 1395w–23(m)(4).

[212] Not all hospitals were eligible; psychiatric, rehabilitation, long-term care hospitals were ineligible. 42 C.F.R. § 412.23.

[213] 42 U.S.C. § 1395ww(n)(2); EHR INCENTIVE PROGRAM, MEDICAID HOSPITAL INCENTIVE PAYMENTS CALCULATIONS (2013), https://www.cms.gov/regulations-and-guidance/legislation/ehrincentiveprograms/downloads/mln_medicaidehrprogram_tipsheet_ep.pdf; EHR INCENTIVE PROG. & CMS, MEDICAID HOSPITAL INCENTIVE PAYMENTS CALCULATIONS (2013), https://www.cms.gov/Regulations-andGuidance/Legislation/EHRIncentivePrograms/Downloads/MLN_TipSheet_MedicaidHospitals.pdf.

[214] Medicare reduced payments by the 25% in 2015 (reporting period 2013), 50% in 2016 (reporting period 2014), and 75% in and after 2017 (reporting period 2015). *See* 2018 MEDICARE ELECTRONIC HEALTH RECORD (EHR) INCENTIVE PROGRAM PAYMENT ADJUSTMENT FACT SHEET FOR HOSPITALS (2017), https://www.cms.gov/newsroom/fact-sheets/2018-medicare-electronic-health-record-ehr-incentive-program-payment-adjustment-fact-sheet-hospitals. "This payment adjustment is applied as a reduction to the applicable percentage increase to the Inpatient Prospective Payment System (IPPS) payment rate, thus reducing the update to the IPPS standardized amount for these hospitals." *Id.*; *see* 42 U.S.C. §§ 1395ww(b)(3)(B)(ix), 1395f(l)(4) (establishing downward payment adjustments under Medicare, beginning with FY 2015, for eligible hospitals and CAHs that do not successfully demonstrate meaningful use of CEHRT for certain EHR reporting periods); *see also* Ian Ayres & Amy Kapczynski, *Innovation Sticks: The Limited Case for Penalizing Failures to Innovate*, 82 U. CHI. L. REV. 1781, 1822 (2015) (arguing that penalties serve as a valuable incentive tool, including in the medical provider context).

[215] Medicare Access and CHIP Reauthorization Act of 2015, § 101(b)(1)(A), Pub. L. No. 114-10, 129 Stat. 87 (codified at 42 U.S.C. § 1305). Hospitals in Puerto Rico were an exception, but the CMS made clear that "in no case may any Medicaid eligible hospital receive an incentive after CY 2021 (§ 495.310(f), 75 FR 44319)." Changes for Hospitals and Other Providers, 85 Fed. Reg. 58,966 (Sept. 18, 2020).

[216] *See supra* note 214. One article suggests the amount paid out as of 2015 was $28.1 billion, but I could not validate that number. Stephen T. Mennemeyer, Nir Menachemi,

This included over $8.6 billion to eligible providers,[217] over $475 million to Medicare Advantage organizations,[218] and over $15 billion to eligible hospitals.[219]

While a price tag of nearly $4 billion per year seems expensive, it was effective.[220] Just how effective is another question. Research shows that hospitals eligible for the subsidies adopted EHR at greater rates than those that were ineligible. But the increase was modest (16.5% adoption per year for eligible hospitals versus 5.5% for ineligible hospitals) and had a more pronounced effect on for-profit hospitals than on not-for-profit hospitals.[221] This effect, however, didn't appear to hold for ambulatory (outpatient) care centers.[222] Despite its uncertain effects, Congress decided to

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Saurabh Rahurkar & Eric W. Ford, *Impact of the HITECH Act on Physicians' Adoption of Electronic Health Records*, 23 J. AM. MED. INFORMATICS ASS'N 375, 375 (2016).

[217] *See EP Recipients of Medicare I Incentive Payments (ZIP) (File 1 of 2)*, CTRS. FOR MEDICARE & MEDICAID SERVS., https://www.cms.gov/Regulations-and-Guidance/Legislation/EHRIncentivePrograms/DataAndReports (last visited Apr. 23, 2022) (showing calculations in 2012 equaling $2,851,324,173.83 and calculations in 2013 equaling $2,568,028,821.01); *EP Recipients of Medicare I Incentive Payments (ZIP) (File 2 of 2),* CTRS. FOR MEDICARE & MEDICAID SERVS. https://www.cms.gov/Regulations-and-Guidance/Legislation/EHRIncentivePrograms/DataAndReports (last visited Apr. 23, 2022) (showing calculations in 2014 equaling $1,890,620,970.41, in 2015 equaling $948,403,852.66, and in 2016 equaling $422,403,778.59).

[218] *See Medicare Advantage Organization Providers Payments (ZIP),* CTRS. FOR MEDICARE & MEDICAID SERVS., https://www.cms.gov/Regulations-and-Guidance/Legislation/EHRIncentivePrograms/DataAndReports (last visited Apr. 23, 2022) (citing MAO incentive totaling $475,772,506.27).

[219] *See EH Recipients of Medicare EHR Incentive Payments (ZIP)*, CTRS. FOR MEDICARE & MEDICAID SERVS.), https://www.cms.gov/Regulations-and-Guidance/Legislation/EHRIncentivePrograms/DataAndReports (last visited Apr. 23, 2022) (providing calculations of incentive payments totaling $15,182,882,175.39 from 2012 to 2016).

[220] *See* Julia Adler-Milstein & Ashish K. Jha, *HITECH Act Drove Large Gains in Hospital Electronic Health Record Adoption*, 36 HEALTH AFFS. 1416, 1419, 1421 (2017) (finding statistically significant differences between adoption rates of EHR by eligible hospitals (16.5% per year) and ineligible hospitals (5.5% per year)); *see also* Daniel Walker, Arthur Mora, Mollye M. Demosthenidy, Nir Menachemi & Mark L. Diana, *Meaningful Use of EHRs Among Hospitals Ineligible for Incentives Lags Behind That of Other Hospitals, 2009–13*, 35 HEALTH AFFS. 495, 495–501 (2016) (finding that eligible hospitals grew their EHR from 4.5% in 2009 to 44.3% in 2013 while ineligible hospitals rose only modestly during the same period (psychiatric hospitals from 0% to just under 10%; rehabilitation hospitals from 1.3% to around 15%; and long-term care hospitals from 0.6% to around 12%)).

[221] Adler-Milsten & Jha, *supra* note 162, at 1421.

[222] Mennemeyer et al., *supra* note 216, at 376–77.

continue the program but not the payments, folding the EHR requirements into an existing CMS incentive system.[223]

The blueprint of the meaningful use program, or others like it, could be used to stimulate providers to systematically collect, organize, and disseminate information about off-label uses. Like the meaningful use subsidy, an "off-label subsidy" would require a system to capture, organize, and publish off-label uses.[224] Whether this subsidy should specify the precise infrastructure necessary to generate this information is something Congress or federal agencies should study.[225] At a minimum, however, the off-label subsidy would specify the kinds of information collected, the form in which it should be collected, and the terms by which it should be disseminated to a centralized government database, which should, to the greatest extent possible, be made available to enterprising third-parties and to the public at large.[226] After a sufficient period

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[223] Many of the requirements for the subsidy, however, have been folded generally into the Medicare Quality Payment Program (MQPP) and specifically into the Merit-Based Payment System (MIPS). Centralized Partnership Audit Regime, 83 Fed. Reg. 41,968 (Aug. 18, 2018). Under the MQPP, Medicare rewards of penalizes providers reimbursement based on their compliance with MQPP requirements. *See* CHIP Act, Pub. L. No. 111-3, § 101(b)(1)(B), 123 Stat. 8, 11 (2009) (retaining meaningful use determinations for merit-based incentive payments); 41 C.F.R. § 414.1415 (2020) (detailing the Merit-Based Incentive Payment System and Alternative Payment Model Incentive).

[224] "Publish" here does not necessarily mean publication in peer reviewed journals. It means something closer to "making publicly available the information in a format that would normally be accepted by a peer-reviewed journal." This avoids the problem of studies that journals are unlikely to publish confirming the null hypothesis.

[225] One issue that should be studied is how much implementation costs are or should be offset by existing EHR systems.

[226] This proposal folds nicely into a noted area of concern for the FDA: how to generate more reliable information that can be used to assess safety and efficacy. *See* FDA RWE FRAMEWORK, *supra* note 160, at 16–17 (stating the importance of examining data relevance to determine the full range of outcomes for studies on health ailments). It might also be an opportunity for the FDA to make headway into specifying a uniform format for IEHR—a problem that is particularly important as the FDA reviews more EHR information. *Id.* at 17–18. Under the RWE Program, the FDA is also considering data standards for RWE. *Id.* at 25. Making data available publicly raises privacy-related concerns under the Health Insurance Portability and Accountability (HIPAA) Act of 1996, Pub. L. No. 104-191, 110 Stat. 1936 (1996) (codified primarily in Titles 26, 29, and 42 of the United States Code); 45 C.F.R. § 164.306 (2020). Most of these concerns, however, can be swept away under one of the many exceptions to HIPAA protections, including disclosures required by law and for public health activities and purposes. 45 C.F.R. § 164.512(a)–(b). Any ancillary privacy-related concerns could be addressed by the agency charged with collecting the information. One potential

of time, the incentives for the off-label subsidy—like the meaningful use subsidy—could be folded into the existing CMS payment system.

Depending on the goals of the program, the off-label subsidy might also address the structural changes needed to conduct reliable prospective observational studies or pragmatic clinical trials. The subsidy could specify payments for setting up and conducting observational studies. Compared to clinical trials, observational studies and pragmatic clinical trials are cheaper and are more feasible for smaller, less sophisticated providers.[227] Maintaining the knowledge infrastructure for these trials may be a particularly important aspect of leveraging innovative new uses—testing them out before running full-on clinical trials. Maintaining provider incentives to continue observational studies, however, might cost more than the meaningful use subsidy. Unlike the fixed costs of adopting EHR, the fixed costs of conducting observational studies are higher and do not decrease with the same effect as do those associated with EHRs. If this strategy is pursued, it will require commitment to a permanent and more expansive role for the government in pharmaceutical drug development.

Using an existing government program has several benefits. First, there is a ready-made framework on which to build. In the course of constructing this framework, the CMS has acquired specialized knowledge about how to implement subsidies, which providers might respond to them, and how to close the existing incentive gaps. Second, the subsidy appears to be relatively successful, at least as to some providers.[228] While it's difficult to extrapolate the effect of this subsidy to one directed at off-label use, it's not unreasonable to assume that a similar subsidy would have similar effects. At the very least, then, providers would probably seek the economic benefits of collecting information in the manner specified by the law. And the benefit here is likely to be much stronger than in the case of EHRs. In the context of EHRs, remember, providers were already beginning to adopt the relevant technology. But the issue for off-label uses is a collective action

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solution, for example, would be to restrict access to information disclosed to the centralized database, leaving only claims data completely publicly accessible.

[227] *See infra* note 292.

[228] *See supra* notes 203204.

problem: providers are not converging on a uniform set of standards for data collection and formatting. The subsidy would help to do so. Finally, to the extent that some fixed costs involve technological capacity or professional know-how, subsidizing those costs might lower the total fixed costs over the long run.

With the meaningful use subsidy, the opposite worry arose because not all providers were eligible to participate: driving down the cost of EHR technology placed ineligible providers in a position to purchase a lower-cost, inferior good. By reducing prices, the subsidy may have caused more inefficiency, or at least might not have done much to increase it.[229] It is not clear how this might affect information collection of off-label uses. An off-label use subsidy would be directed primarily at collection, organization, formatting, and dissemination of data on off-label use. As such, the quality of the underlying technology used to capture that data is less important, provided that it collects data with roughly the same accuracy and information output as superior systems.

Another shortcoming of the meaningful use subsidy was its exclusion of certain providers. While many providers—including small, office-based providers were eligible[230]—some hospitals were not. Psychiatric, rehabilitation, and long-term care hospitals were ineligible.[231] Following this path for off-label use would be a significant missed opportunity, particularly because a large percentage of off-label use occurs in psychiatry.[232] Additionally, many rehabilitation hospitals treat patients with no known cures or few treatments, such as TBI, stroke, and chronic pain.[233] Tracking and studying off-label use in these settings is crucial to obtaining information about both identification and validation of new uses. They should, therefore, be eligible for the off-label subsidy.

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[229] *See, e.g.*, Mennemeyer et al., *supra* note 216, at 378 (discussing the effect of the subsidy on the adoption rate of the "Any EHR system").

[230] *See* Brian K. Bruen, Leighton Ku, Matthew F. Burke & Melinda Beeuwkes Buntin, *More Than Four in Five Office-Based Physicians Could Qualify for Federal Electronic Health Record Incentives*, 30 HEALTH AFFS. 472, 474 (2011) (discussing the eligibility of small offices for federal electronic health record incentives).

[231] *Id.* at 477.

[232] See *supra* notes 11, 18 and accompanying text.

[233] Medicare has a specific definition of "rehabilitation hospital" for coverage and reimbursement purposeI42 U.S.C. §§ 1395x(e), 1395ww(j)(1); 42 CFR §§ 482.1 *et seq.*, 412.20, 412.604.

Further study is needed, of course, to evaluate the costs and benefits of using a subsidy modeled on the one used for EHRs. This would require evaluating, among other things, eligibility, who could qualify, the benchmarks required for qualification, and the structure, amount, and duration of the subsidy. In the next Section, I explore some of the requirements that are crucial to any government subsidy and how they might be implemented in the context of a new kind of subsidy: market inclusivity.

C. NEW GOVERNMENT PROGRAMS: MARKET INCLUSIVITY

Existing government programs provide an off-the-shelf framework that reduces implementation costs. But, as we've seen, there are still challenges to applying an existing framework off-label, as it were: different problems may require modification of existing systems or different systems altogether.[234] While the last Section describes the former, this Section describes the latter: what I call the *market inclusivity* subsidy (MI Subsidy). Under this program, providers who implement systems to generate, collect, organize, and disseminate information about off-label prescriptions are entitled to obtain a direct government payment for each off-label use they track, with the size of the payment dependent on the frequency and detail with which providers track it. Below I explain how this potential solution would leverage existing provider capabilities, which vary by size and type, to collect, organize, and disseminate information about off-label uses.

1. Eligibility & Qualification. Like the meaningful use subsidy, the MI Subsidy would have three components: eligibility, qualification, and payment. Eligibility represents the possible universe of individuals or entities that could obtain the subsidy. Given that the subsidy is designed to collect as much information as possible about off-label uses, in principle any provider should be eligible.

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[234] Providers aren't the only option, either. *See* Eisenberg, *The Problem of New Uses*, *supra* note 25, at 739 (discussing the limited options that providers have when the FDA sequesters valuable data). More recently, Congress has tried to combat this problem through increased monitoring and information collection. *See generally* The Food and Drug Administration Amendments Act of 2007, Pub. L. No. 110-85, 121 Stat. 823 (codified as amended in various sections of 21 U.S.C.). As I explain below, this includes the Sentinel Initiative.

Eligibility is a necessary but not sufficient condition for obtaining the subsidy. Eligible providers must still qualify for the subsidy, which they can do by meeting conditions specified by the government. By setting qualifications, the government forces eligible providers seeking the subsidy to engage in the desired activity. Here the desired activity is to collect information about off-label uses, organize it, and disseminate it. Just what kind of information—and the manner in which it should be collected, organized, and disseminated—is open to debate.

But the debate is not without boundaries. To solve or mitigate both Problems, information about off-label uses must have certain characteristics. First, the data must be of a minimum type and quantity. Information must contain, for example, the patient's diagnosis and the prescribed drug, including the dose, method of administration, and frequency. It may also include other information, such as previous prescriptions (both on- and off-label), patient compliance, follow ups, adverse reactions, and other drugs the patient is taking.

Second, this data must be uniformly formatted. While uniformity isn't a logical necessity, it is a practical one. Without it, efficient data-mining and analysis would be impossible. Uniformly formatted data enables information pooling and, hence, analysis of a single dataset.[235] A requirement of some minimum kind or amount of data increases the value of the dataset: the more information required, the more valuable the data set. At the same time, additional requirements increase costs to providers: the higher the minimum threshold, the greater the initial fixed costs to gather it.[236] To determine the optimal formatting and minimum requirements, the relevant federal agencies could form a commission, conduct a pilot study, or both.[237]

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[235] *See* Joachim Roski, George W. Bo-Linn & Timothy A. Andrews, *Creating Value in Health Care Through Big Data: Opportunities and Policy Implications*, 33 HEALTH AFFS. 1115, 1116 (2014), https://www.healthaffairs.org/doi/pdf/10.1377/hlthaff.2014.0147.

[236] The relationship is not exactly one-to-one. Some data might be quite easy to get (e.g., low initial fixed costs) because of existing systems, while other data may be expensive to obtain (e.g., high initial fixed costs).

[237] This might be an opportunity for the FDA to make headway into specifying a uniform format for EHRs—a problem that is particularly important as the FDA reviews more EHR information. *See* FDA RWE FRAMEWORK, *supra* note 160, at 17–18 (explaining that tools

Third, uniformly formatted data must be communicated or disclosed to the public (or a public agency) for the system to function properly. The government, and even private actors, can't realize the benefits of data collection if the data are not available for analysis. And, if data collection is done right, a dissemination or publication requirement has the potential to cure the market failure in diffusion of innovative new uses.[238] Put another way, if the program causes providers to collect information on innovative new uses, the dissemination requirements will ensure that those new uses are diffused.

Dissemination could take a variety of forms. One option is to disclose data to the FDA, either by using an existing information-collection program, such as the Sentinel Initiative,[239] or by developing a new one, either within the FDA or in a collaborative effort with the CMS. Another is requiring providers to publish (some limited) data on their own websites, a government website, or a third-party service. Some combination of these—and others—is also possible.[240]

Whatever and however information is produced, it's important to balance government expectations with provider capabilities. In general, smaller providers—which constitute around 50% of all providers[241]—are less sophisticated, have less technology, and have fewer resources than large providers. Data collection requirements for small providers, then, should probably be less onerous than those for larger providers. One can imagine a program where small providers have fewer system and data output obligations (e.g.,

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must be developed in order to induce more effective use of RWE)*; see also id.* at 25 (stating that under the RWE Program, the FDA is also considering data standards for RWE.).

[238] The CURE ID program attempts to fix this market failure by decentralized data gathering. *See* CURE Drug Repurposing Collaboratory, *supra* note 179 (explaining that CURE ID is dedicated to capturing clinical outcome data to advance drug repurposing and inform future clinical trials).

[239] *See* FDA RWE FRAMEWORK, *supra* note 160, at 29 (defining the Sentinel Initiative as "a long-term effort to create a national electronic system for monitoring FDA-regulated medical products").

[240] There are HIPAA concerns with publishing data publicly that could counsel against a dichotomous or layered approach in which some basic claims level data are published and other data are submitted to the government for research purposes.

[241] *See* Kane, *supra* note 178, at 5 ("In 2018, 56.5 percent of physicians worked in practices with 10 or fewer physicians . . . .").

minimum requirements to track and disseminate prescription, adverse reactions, drug, dose, formulation, diagnosis, existing medications, and refill requests) than large providers (e.g., minimum requirements to implement a formulary, track all off-label uses, patient follow up, off-label requests, etcetera, and disseminate that information). Small providers could still be encouraged to collect information required of large providers, as explained below, through additional incentive mechanisms, like bonus payments, that are built into the subsidy program.

With respect to large providers, Congress could leverage the significant resources and structure of institutions like hospitals, including P&T committees, to collect more data and to implement evidence-based reforms for off-label uses. Congress might, for example, mandate that larger providers build out and maintain a dynamic formulary system. This formulary system could include, among other things, a process for requesting, reviewing, approving, and tracking off-label uses, as well as one for disseminating all of this information in an organized and uniformly formatted manner.[242]

Although some minimum requirements for a formulary system are desirable, formulary systems needn't be identical—at least not at first. Some amount of experimentation is beneficial, and based on current practices, we should expect it to occur. Formulary and P&T procedures and practices vary quite widely by institution.[243] And although most hospitals have a formulary and a P&T committee,[244] not many providers have systems in place to capture the needed

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[242] Not all off-label uses will be off-formulary; some off-label uses will be on the formulary.

[243] *See generally* Anagnostis et al., *supra* note 166 (detailing different member institutions' standards of practice).

[244] Formularies are required to be eligible for Medicare payments. *See* 42 C.F.R. § 482.25 (2020) ("A formulary system must be established by the medical staff to assure quality pharmaceuticals at reasonable costs."). The regulations don't require hospitals to establish a P&T committee specifically. *See generally* 42 U.S.C. § 1395bb; 42 C.F.R. § 482 *et seq*. But as part of the eligibility process, Medicare allows providers to obtain accreditation to avoid more onerous state surveys. In essence, the government has farmed out the eligibility-determination process to various organizations, the most prominent of which is the Joint Commission.

data.[245] This is true even though providers are quite adept at collecting information for non-formulary (and off-label) uses.[246]

It's also not that surprising. Each provider may have different needs and institutional structures, politics, and financial outlooks. Because of these differences, each provider is best positioned to evaluate its own needs and develop a system suited to it. As more providers seek MI Subsidies, practices will shift and become more efficient. Providers that comprise numerous hospitals or practice groups may seek to integrate or consolidate their formularies and P&T committees as the benefits of doing so become apparent.[247] Eventually, the FDA (or a similar agency) could commission a study on the practices of providers and, based on its findings, use its rulemaking authority to standardize and modernize market inclusivity requirements.[248]

2. Market Inclusivity Subsidy. The third component of market inclusivity is a subsidy. Eligible providers that qualify for a MI Subsidy would obtain a direct payment for all "covered drugs."[249] A "covered drug" means any drug used off-label that the provider tracks with the specified system, as explained in more detail below.[250] In general, providers that track more drugs with greater

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[245] *See* Anagnostis et al., *supra* note 166, at 412–13 (showing that although non-formulary use seems to be better tracked, *what* providers "tracked," varies throughout the data). Formularies, of course, may include many off-label uses that may not be tracked with regularity.

[246] *See* Anagnostis et al., *supra* note 166, at 412 (describing tracking methods for non-formulary medication use).

[247] Large healthcare networks, which continue to grow, operate like franchises and impose formulary requirements on their "members."

[248] Traditional clinical trials use standardized procedures for information collection and recording. *See, e.g.*, An-Wen Chan et al., *SPIRIT 2013 Statement: Defining Standard Protocol Items for Clinical Trials*, 158 ANNALS INTERNAL MED. 200, 202 tbl.1 (2013) (recommending plans for data collection, management, and analysis as part of the standard protocol for clinical trials). The FDA could apply a similar approach here. In the initial phases, the FDA could roll out a pilot program to determine feasibility and areas for improvement.

[249] The average cost would likely reflect private pricing schemes under Medicare Part D. But it would also include the costs of drugs under Medicaid.

[250] If the provider intends to claim tax credits for clinical trial research using this system, rules might also require the system to include a process integrating the system into clinical trials. The FDA has already begun promoting the integration of clinical trials into practice settings. *See* U.S. FOOD & DRUG ADMIN., FRAMEWORK FOR FDA'S REAL-WORLD EVIDENCE PROGRAM 10–11 (2018) [hereinafter FDA RWE FRAMEWORK], https://www.fda.gov/media/120060/download.

detail would obtain a greater subsidy than those who track fewer drugs with less detail. This should induce providers to track as many off-label uses as possible while accounting for the different capabilities of providers to track and monitor off-label use. The overall benefits of this subsidy could be significant given that patients fill over four billion prescriptions per year.[251] The exact amount of the MI Subsidy, however, should be set only after sufficient research to determine the optimal subsidy to induce providers to engage in the desired activity.

Without that research, though, it is possible to offer a few comments about how this payment system might be structured. First, economic incentives should drive providers to collect as much information about off-label uses as possible. This will ensure that the system captures not only information about existing off-label uses but also information about new, innovative off-label uses. Second, payments should be progressive: the more information providers collect, and the more useful it is, the larger the payment should be. Third, the incentive should encourage providers to disseminate, as well as to collect and organize as described in Section III.B, the off-label information that they track.

One method for achieving these aims is a point-based system. Under a point-based system—such as the one the CMS currently uses to incentivize alternative payment structures and quality improvements[252]—the government scores entities along the desired metrics by assigning them points based on compliance with specified requirements.[253] Various weighting techniques, along with "bonus" points, can be used to emphasize some metrics over others or to tailor incentives to different providers. Small providers—

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[251] *Total Number of Retail Prescriptions Filled Annually in the United States from 2013 to 2025 (In Billions)*, STATISTA, https://www.statista.com/statistics/261303/total-number-of-retail-prescriptions-filled-annually-in-the-us (last visited Apr. 24, 2022).

[252] *See* 42 C.F.R. §§ 414.1300–414.1465 (2020) (setting incentive payments for providers that participate in eligible alternative payment models); 42 U.S.C. § 1395w–4 (describing a fee schedule-based payments, a quality reporting system, and a merit-based incentive payment system).

[253] The CMS, for example, evaluates based on "quality performance," "cost performance," "improvement activities performance," and "Promoting Interoperability performance," the last of which is the EHR subsidy that the CMS folded into its requirements after the original subsidy expired. 42 C.F.R. § 414.1380(a)(1) (2020).

office-based practices with one or two physicians, for example[254]—can receive bonus points for taking actions that larger providers must take as a matter of course.[255] Generally speaking, though, entities that excel on the specified metrics receive more points than those that perform poorly. Points are then compiled, weighted, and summed.[256]

Currently, the CMS uses the sum to adjust providers' Medicare Part B payments: entities with high scores receive more payments than those that receive lower scores.[257] Weighting can be made according to point totals, point totals relative to historical "benchmarks," or some combination of the two.[258] In some cases, low performing entities will not score any points (i.e., will not receive payment for that metric) or may be penalized if they don't meet minimum point requirements in that category.[259] Maximum or "top out" payments can also be set for providers that score the maximum number of points in any given year or in consecutive years.[260]

Congress could use a similar, but more robust, system to incentivize providers to collect, organize, and disseminate information about off-label uses. This probably would require creating a new subsidy system that falls outside the scope of the existing point-based system—perhaps even outside of the CMS—which incentivizes providers by making adjustments to their payments under Medicare Part B.

There are several reasons for devising a new subsidy system rather than folding new requirements into an existing program. The

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[254] The CMS, for example, awards "bonus points . . . in small practices that submit data on at least 1 quality measure." *Id.* § 414.1380(a)(1)(i).

[255] Bonus points are also given for treating complex patients. *Id.* § 414.1380(c)(3).

[256] *See id.* § 414.1380(c) (providing final score calculation formulas).

[257] *See* 42 C.F.R. § 414.1405 (providing payment adjustment factors based on how their final score compares to performance thresholds and applying the adjustment factors to Part B payments); *see also* 42 C.F.R. § 414.1380(b)(1)(ii) (overviewing benchmark requirements).

[258] *E.g.*, 42 C.F.R. § 414.1380(c) (providing methodology by which CMS weights and reweights performance categories). This is similar to the concept of "yardstick competition." Ian Ayres & Amy Kapczynski, *Innovation Sticks: The Limited Case for Penalizing Failures to Innovate*, 82 U. CHI. L. REV. 1781, 1786 (2015).

[259] *See, e.g.*, 42 C.F.R. § 414.1380(a)(1)(i), (c) (describing how, "for the quality performance category, measures are scored between zero and 10 measure achievement points" and explaining the corresponding formula for calculating the final score of an eligible clinician).

[260] *See, e.g.*, 42 CFR § 414.1380(b)(1)(iv) ("CMS will identify topped out measures in the benchmarks published for each Quality Payment Program year.").

first is that reimbursements under Medicare Part B may not be sufficiently tied to the activity that the subsidy is designed to address. The aim of the MI subsidy is to reduce the overall incidence of improper prescriptions and increase the number of proper prescriptions, not to improve care or service delivery *under Medicare Part B*.[261] Relatedly, providers do not generally receive compensation for prescription drugs;[262] compared to services, providers receive almost no money for prescription drug costs.[263] Folding additional payment adjustments into Part B, therefore, might unduly affect the existing incentives (i.e., Medicare Part B adjustments). Finally, although many providers serve individuals whom public insurance covers, not all serve a sufficiently large number of them. To capture as many uses as possible requires paying as many people as possible.[264]

A new point system could take many forms. In the next few paragraphs, though, I try to roughly sketch one of these possible forms, as well as some of its potential drawbacks. In this system, recall, providers can qualify by meeting certain minimum requirements for collecting, formatting, organizing, and disseminating data.[265] Each of these categories, as well as others, could serve as potential metrics along which to evaluate providers and incentivize them to collect, organize, and disseminate more data with greater granularity. Within the collection metric, for

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[261] Reducing unnecessary prescriptions may reduce costs under Medicare Part B because patients may experience fewer adverse events and need less care. The primary savings, however, will rebound to Medicare Part D, consumers, and payers.

[262] The CMS does reimburse some drug costs to providers under Medicare Part B and uses an incentive to induce providers to treat large proportions of low-income patients. 42 U.S.C. § 256(a)(1)–(3). The GAO recently found that the discount seemed to encourage prescribing higher cost drugs. U.S. GOV'T ACCOUNTABILITY OFF., GAO-15-442, MEDICARE PART B DRUGS: ACTION NEEDED TO REDUCE FINANCIAL INCENTIVES TO PRESCRIBE 340B DRUGS AT PARTICIPATING HOSPITALS (2015), https://www.gao.gov/products/GAO-15-442.

[263] Providers that obtain certain drugs can obtain payments under Medicare Part B, but this is not, by and large, the majority of prescription drug costs. *See* Cole Werble, *Medicare Part B*, HEALTH AFFS. (Aug. 10, 2017), https://www.healthaffairs.org/do/10.1377/hpb20171008.000171/full/.

[264] Casting a wider net, of course, will be more expensive. And it may raise sustainability concerns for the program.

[265] When the Meaningful Use Program began, its first stage had fifteen "core objectives" that incentives were designed to induce eligible professionals to satisfy. 42 CFR § 495.20(d) (2020).

example, providers could earn points for performance in categories like "prescription capture," "patient follow-up," "symptom tracking," "event tracking," and "outcomes." Providers that captured only the drug and the off-label use for which it was prescribed would receive the minimum number of points. Additional points could be awarded for how well or poorly providers tracked patient compliance, prescription changes (e.g., dosage, administration, discontinuation, and additional/alternative medications), and event reporting (e.g., symptom reduction and side-effects or adverse events). A separate category of points, or bonus points, could be used for "innovative" new uses that a provider captures and disseminates.

Similar point categories could be developed for organization and dissemination (by exceeding minimum requirements and meeting additional standards). Providers, for example, could receive points for disclosing the minimum level of data and additional points for publishing some of the data on public-facing websites or in peer-reviewed journals, disseminating it to drug compendia or even to insurance providers. Eventually, metrics could be "benchmarked" to past performance and subsidies allocated based on performance relative to the benchmark.

Rewards can be a powerful motivator, but in appropriate circumstances, penalties can spur the desired activity as well. It is, therefore, worth considering how the new program might penalize providers for noncompliance.[266] Compared to "carrot" like subsidies, "stick" like fines are much less costly.[267] And they are also useful for specifying and enforcing a minimum baseline of activity below which providers can't fall.[268] Like the existing EHR Program, this suggests that providers should be *mandated* to collect some minimum quantum and quality of information or else face penalties. Unlike the EHR program, however, penalties under the MI subsidy program would not result in decreased Medicare adjustments;

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[266] *See* Ayres & Kapczynski, *supra* note 214, at 1822 (describing how using potential penalties incentivized producer innovation as it relates to Medicare's hospital reimbursements).

[267] *See id.* at 1799–1800 ("Most importantly, . . . sticks do not need to be paid. Carrots, by contrast, can be used up—if they are paid as a reward to one person, they cannot also be paid to another.").

[268] *See id.* at 1803.

rather, they would come as some other form of liability, such as a fine.

There are, of course, drawbacks to using penalties to spur behavior. If compliance costs are not identical for all actors, penalties may disproportionately affect those who are least able to comply.[269] Actors who have difficulty meeting minimum requirements may be forced to exit the market or to change their business models in socially undesirable ways. This problem could arise in the off-label information context if minimum requirements are set too high for some or all providers. Small providers, in particular, may be less equipped to absorb the costs of implementing a new off-label information system. Penalizing them for failing to implement it could have serious negative effects, such as reductions in quality of care or staff.

Additionally, sticks are difficult to calibrate correctly when the expected social value of the desired activity isn't known.[270] Tying cost to expected social value is challenging because estimating the existing cost of unnecessary or improper prescriptions is very difficult—partly because there isn't good quality information about off-label prescriptions.[271] But the government doesn't actually have to know the expected social value of the information generated, and it probably couldn't reliably estimate it if it tried. It can, instead, determine the expected cost *to the provider* and set a penalty that is sufficiently high to induce the provider to engage in the desired activity but small enough that it will not affect the quality of the provider's existing services (or have other negative effects).

These difficulties suggest that a better approach might be a program that induces providers to participate (by promising payment) and then later penalizes participating providers for noncompliance with program standards (by imposing discontinuing payment or imposing a fine). Dangling a reward to induce provider participation will encourage providers' self-selection into the

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[269] *See id.* (describing how sticks may work best when "citizens have more or less equal compliance costs" as opposed to more complex situations).

[270] *See id.* at 1802.

[271] *See, e.g.*, STUART WRIGHT, DEP'T OF HEALTH & HUM. SERVS., MEMORANDUM REPORT: ENSURING THAT MEDICARE PART D REIMBURSEMENT IS LIMITED TO DRUGS PROVIDED FOR MEDICALLY ACCEPTED INDICATIONS (2011) [hereinafter Wright, *Medicare Part D Reimbursement*] (noting that there is a lack of information for off-label prescriptions).

program based on the projected economic benefit. Once in the system, provider behavior can be influenced by increasing or decreasing payments based on their performance. Rewarding participation would also enable a more effective system of sticks: because providers have already selected into the system, fining providers that fail to meet the minimum requirements is less likely to have the undesirable consequences described above.

Subsidizing costs this way, however, may also lead to socially undesirable prescribing patterns. Providers may prescribe and track more drugs off-label to obtain greater subsidies. While this risk is real, there are several existing mechanisms that disincentivize prescribing in this manner. One is tort law. Physicians who prescribe in ways that are detrimental to patients' health face legal liability. Another is the physician's professional obligation.[272] Ethics rules require physicians to treat patients in an ethical manner; prescribing drugs unnecessarily and solely for profit runs afoul of these rules.[273] Physicians who violate ethics rules risk losing their license.[274]

Costs imposed by law and professional organizations, however, may not be a sufficient disincentive. Legally, for example, it is quite difficult to prove medical negligence based on an off-label use.[275] And physicians can avoid professional sanction by pointing to some medical rationale for prescribing off-label. To combat this, subsidies could be tied to the average rate of prescribing off-label. With

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[272] *See, e.g.*, Medical Practice Act of 1987, 225 ILL. COMP. STAT. §§ 60/2, 60/10 (delegating the power to regulate the practice of medicine to the Illinois Department of Financial and Professional Regulation); 68 ILL. ADMIN. CODE tit. 68 §§ 1285.200–1285.280 (2005) (stating regulations governing practice of medicine, including standards for ethical conduct and the procedures for disciplinary action).

[273] *See, e.g.*, ILL. ADMIN CODE tit. 68, § 1285.240 (2005) (describing standards of unethical or unprofessional conduct in medical practice).

[274] *See, e.g.*, Medical Practice Act of 1987, 225 ILL. COMP. STAT. § 60/22(A)(18) (listing "[p]romotion of the sale of drugs . . . in such manner as to exploit the patient for financial gain" as a violation of professional conduct punishable by license revocation).

[275] *See, e.g.*, Philip M. Rosoff & Doriane Lambelet Coleman, *The Case for Legal Regulation of Physicians' Off-Label Prescribing*, 86 NOTRE DAME L. REV. 649, 666 (2011) (noting off-label malpractice claims are rare in published cases). The more exotic the use, the greater the threat of liability. *See* James O'Reilly & Amy Dalal, *Off-Label or Out of Bounds? Prescriber and Marketer Liability for Unapproved Uses of FDA-Approved Drugs*, 12 ANNALS HEALTH L. 295, 317 (2003); Johnson, *supra* note 95, at 68 (noting off-label use can become the standard of care, making physicians potentially liable for *not* prescribing off-label).

sufficient data, the administering government entity could calculate the average number of off-label prescriptions for a given use and break out the data by provider type. It could then specify an "allowable" range around the average prescription volume per provider type. Providers whose prescription volume fell outside of a specified range wouldn't qualify for reimbursement.

An alternative strategy would use additional inducements to curb socially undesirable behavior. Rather than punish providers for overprescribing, this strategy would reward them for tracking information that is most needed. The administering agency could, for example, award more points for off-label information for rare diseases, understudied diseases, or promising uses. The predicted effect, following the logic above, would be more off-label prescriptions (and information) and a corresponding increase in the supply of information about the safety and effectiveness of off-label uses in the areas where they are most needed or most likely to be useful.

One final, but important, question is how long this subsidy should last. Like with the meaningful use subsidy, the MI Subsidy should be responsive to the costs associated with developing, implementing, and maintaining the required system. The largest cost to providers will be implementing the information system. Once implemented, the costs of maintaining the system are unlikely to outpace the fixed costs of creating it. While this may change with more sophisticated data collection (e.g., large providers), continuing to collect information will be much less costly after providers implement data-collection systems. The precise amount of this subsidy, how it should be maintained, and whether it should be phased out entirely are all questions that are beyond the scope of this Article. At the very least, however, Congress should consider various options for continuing the subsidy, including phasing it out completely, folding the subsidy into existing incentives, or requiring renewal certifications for continued payments.

D. TAX CREDITS AND GRANTS

Direct government payments are not the only kind of subsidy available to incentivize provider information collection, organization, and dissemination. Tax incentives also can induce providers to (a) institute information collection, organization

systems, and procedures to capture off-label use, frequency, and effects; or (b) generate data from clinical trials and (prospective) observational research.[276] Because I focused mainly on (a) in the previous two Subsections, here I limit the discussion to (b). At bottom, tax incentives are a way to get private parties to do things by paying them.[277] There are two kinds of tax incentives: credits and deductions. Tax credits provide a dollar-for-dollar reduction in tax liability.[278] Tax deductions, on the other hand, reduce the taxpayer's taxable income.[279] Both can represent a government subsidy to engage in a particular activity.[280]

Tax incentives are not new to pharmaceutical development. Congress has used them in the past to stimulate production of information about drugs—specifically clinical trial data about drugs used to treat rare diseases.[281] In the Orphan Drug Act (ODA), for

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[276] Here I don't mean to limit "clinical trials" to double-blind, randomized controlled trials. It could also include so-called "practical" clinical trials. *See, e.g.*, Sean R. Tunis, Daniel B. Stryer & Carolyn M. Clancy, *Practical Clinical Trials: Increasing the Value of Clinical Research for Decision Making in Clinical and Health Policy*, 290 JAMA 1624, 1626 (2003).

[277] *See* Daniel J. Hemel & Lisa Larrimore Ouellette, *Beyond the Patents-Prizes Debate*, 92 TEX. L. REV. 303, 307–08 (2013) ("[I]ncentives—like patents—leverage the value of information held by private parties.").

[278] *See Policy Basics: Tax Exemptions, Deductions, and Credits*, CTR. ON BUDGET & POL'Y PRIORITIES, https://www.cbpp.org/research/federal-tax/tax-exemptions-deductions-and-credits (last updated November 24, 2020) ("Taxpayers subtract their credits from the tax they would otherwise owe to determine their final tax liability.").

[279] *See id.* ("[D]eductions indirectly reduce the amount of taxes a filer owes by reducing his or her 'taxable income,' which is the amount of income on which a filer pays taxes.").

[280] Let's assume a taxpayer has $100 in taxable income and is taxed at a rate of 35%. A $35 deduction would reduce the taxpayer's taxable income to $65, which would be taxed at the rate of 35%, for a total tax bill of $22.75. A $35 tax credit, on the other hand, would reduce the taxpayers total tax *liability* of $35 to $0 (100*.35=35-35).

[281] Existing law uses a combination of both deductions and tax credits. *See* David M. Richardson, *Orphan Drug Tax Credit: An Inadequate Response to an Ill-Defined Problem*, 6 AM. J. TAX POL'Y 135, 168–69 (1987) (stating that the federal government agreed to fund "a maximum of 73 percent of the portion of the orphan drug research expenses that constituted 'qualified clinical testing expenses'"); Nina J. Crimm, *A Tax Proposal to Promote Pharmacologic Research, to Encourage Conventional Prescription Drug Innovation and Improvement, and to Reduce Product Liability Claims*, 29 WAKE FOREST L. REV. 1007, 1057 (1994) (noting that the Section 174 deduction did not provide a sufficient incentive to stimulate drug R&D, and as a result, Congress enacted the Economic Recovery Tax Act of 1981 which created the Section 41 research tax credit); William Natbony, *The Tax Incentives for Research and Development: An Analysis and a Proposal*, 76 GEO. L.J. 347, 382 (1987) ("Congress elected to offer businesses a tax credit for increasing (not merely paying) research

example, Congress provided drug companies additional tax incentives that allowed them to claim a tax credit of 50%[282] (later reduced to 25%[283]) of all expenses on human clinical testing of an orphan drug.[284] Companies could avail themselves of this maximum credit only when they performed human clinical trials for orphan drugs.[285]

A similar system could be used to subsidize providers to engage in R&D of new and off-label uses. One option would borrow from the Orphan Drug Act but expand the amount of credit available from 25% to 100% of all human clinical trials and prospective observational studies conducted by providers.[286] Just like the current tax credit for research activities in Section 41 of the Tax Code, this tax credit would apply only to *increased* research

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and experimental expenditures."). *Compare* 26 U.S.C. § 45C (describing a tax credit for clinical testing for certain drugs for certain rare diseases), *with* 26 U.S.C. § 174 (describing a deduction for "research and experimental expenditures"). Two tax credits apply regardless of whether the research in question is for orphan drugs. *See* 26 U.S.C. § 41(a)(1)–(2) (explaining the general rule for calculating the research credit for increasing research activities). In 2014, the Treasury Department issued final regulations concerning Section 174 deductions. *See* Research Expenditures, 79 Fed. Reg. 42,193, 42,194 (July 21, 2014) (clarifying deductions for tangible property but also eliminating some uncertainty regarding whether some drug-related expenses could be deducted, including pilot models). Given that all of the proposed research activities—at least at first—would take place before filing an NDA and concern a drug with an uncertain safety and efficacy profile, they will be deductible under Section 174. *See* Crimm, *supra* note 281, at 1055, 1067, 1069 (arguing that tax incentives should be available for research that does not necessarily lead to new a new drug but nonetheless leads to pharmaceutical advancements).

[282] Orphan Drug Act, Pub. L. No. 97-414, 96 Stat. 2049, 2053 (1983) (codified at 26 U.S.C. § 45(a)).

[283] Tax Cuts and Jobs Act, Pub. L. No. 115-97, 131 Stat. 2133, § 13401(a) (2017) (codified at 26 U.S.C. § 45C(a)).

[284] The Tax Code does not allow for double- or triple-dipping on deductions and credits, but deductions may cover activities that credits do not, and vice versa. *See* 26 U.S.C. § 280C(c)(1) (disallowing deduction for qualified research activities determined as a credit); *id.* § 280C(c)(2) (requiring a like kind reduction in credits where qualified research expenses are capitalized rather than deducted).

[285] *See* 26 U.S.C. § 45C(b)(2)(A) (defining clinical testing as testing carried out under the ODA for rare diseases); *id.* § 45C(b)(2)(B) (defining testing as some types of "[h]uman clinical testing"); *id.* § 45C(d)(1) (defining rare disease or condition); Richardson, *supra* note 281, at 173 (noting ODA was not designed "to foster basic research into the causes of orphan diseases or conditions or to fund or otherwise encourage preclinical testing").

[286] Alternatively, Congress could provide a 100% tax credit and then reduce the other applicable credits by the claimed credit.

activities.[287] Put another way, providers could obtain a tax credit only for those clinical trials and observational studies they wouldn't have otherwise undertaken.

Another option is to benchmark the "base rate" to the initial year the tax credit is claimed. This would allow providers to engage in the same level of research year-after-year without losing the tax credit. Research "increases," in other words, would always be determined by a "base rate" set by the initial year the provider claimed the tax credit.

Although it's not entirely clear that this is the best approach, there are at least three reasons favoring a dollar-for-dollar, fixed-base-amount tax credit. First, providers, unlike pharmaceutical companies, have no way to recoup investment costs.[288] And that's the entire point: information collection and analysis is not something that providers use to generate profits.[289] Second, providers have less financial wherewithal than large pharmaceutical firms to engage in research.[290] Third, existing tax incentives available to pharmaceutical companies may not be available to providers.[291] Whatever the optimal approach, Congress

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[287] *See* 26 U.S.C. § 41(a) (stating that the Section 41 tax credit of 20% for incremental research is available only for "qualified research" expenses exceeding a "base amount"); 26 U.S.C. § 41(d)(1)(A) (noting that obtaining tax credits under Section 41 requires satisfying the definition of R&E expenditure under Section 174); Crimm, *supra* note 281, at 1059–60 (describing prerequisites for the tax credit); *see also* Lily L. Batchelder, Fred T. Goldberg, Jr. & Peter R. Orzag, *Efficiency and Tax Incentives: The Case for Refundable Tax Credits*, 59 STAN. L. REV. 23, 32–42 (2006) (describing refundable tax credits); Crimm, *supra* note 281, at 1076 (stating that tax credits under the ODA are "neither refundable nor recapturable."). It is not clear whether this would make a real difference to providers, who will usually have substantial taxable income. *See* Natbony, *supra* note 281, at 351 (noting that current R&D incentives prejudice companies with no current taxable income). For those with less substantial income, however, the benefits of a refundable tax credit could be quite significant.

[288] It is possible to offer a reward for a provider that produces important research, but it would require significant changes to the drug approval process. *See infra* Section IV.E.

[289] Third parties may still use the publicly available data for profitable uses, of which there are likely to be many. See *infra* note 300.

[290] It may even be worth considering making these tax credits refundable—applicable regardless of whether providers have any taxable income. *See* Hemel & Ouellette, *supra* note 277, at 337 (explaining this feature of tax credits in other jurisdictions).

[291] *See* Crimm, *supra* note 281, at 1052–55 (noting uncertainty of Section 174 deductions for research directed at new products but emphasizing that research that "eliminates uncertainty concerning the development or improvement of a quality product" may be

should consider these differences when deciding the type and amount of any tax credit.

While tax incentives to providers are important, they don't necessarily optimize information generation. For various reasons—size, location, demographics, or sophistication—individual providers may not be able to produce the kind of information we desire. For that reason, effective tax incentives will encourage providers to collaborate.[292] At the very least, the tax incentive structure should not make it less attractive to collaborate than to conduct research individually. Unlike the current tax credit for university research,[293] the tax credit for providers might allow multiple providers to claim a (non-refundable or refundable) tax credit for the relevant portion of the research conducted with other providers.[294]

This is also an opportunity to encourage collaboration between large and small providers[295] or between industry and providers.[296] Providers may work with payors to build out better pricing

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deducted). Given that the research might simply provide more information about a use, and not to a new product, this deduction may not be available. *Id.* at 1052–53.

[292] Practical or pragmatic clinical trials, for example, may require numerous community-based clinics jointly participate. *See* Tunis et al., *supra* note 276, at 1626–27. Sometimes smaller providers may actually provide a more efficient option for clinical trials. *See* Johnson, *supra* note 95, at 96–97.

[293] *See* Crimm, *supra* note 281, at 1072–73 (noting criticism of Section 41(a)(2) credit on grounds it does not "reward research undertaken by R&D consortia or alliances"). Credits can be claimed, however, for the qualified research expenses under Section 41(a)(1). *See* 26 U.S.C. § 41(b)(3)(C) (stating that up to 75% of qualified research expenses paid or incurred by the taxpayer to qualified consortia qualify as contract research expenses and are subject to the 20% credit under Section 41(a)(1)).

[294] This would make any congressional action somewhat more complicated than simply trading on the existing tax credit structure.

[295] *See e.g.*, Charles D. Cobau, *Clinical Trials in the Community: The Community Clinical Oncology Program Experience*, 74 CANCER 2694, 2694 (1994) (describing a program designed to transfer knowledge from large research institutions to small providers).

[296] *See* Eisenberg & Price, *supra* note 44, at 17 (noting that comparativeness studies frequently involve partnering with healthcare payors like insurance companies to leverage large datasets)*; see also* Thomas O. Stair, Caitlin R. Reed, Michael S. Radeos, Greg Koski & Carlos A. Camargo, *Variation in Institutional Review Board Responses to a Standard Protocol for a Multicenter Clinical Trial*, 8 ACAD. EMERGENCY MED. 636, 636–641 (2001) (noting that a local institutional review board (IRB) was inefficient and proposing a nationalized standard for IRB review of multicenter clinical trials).

mechanisms or evidence.[297] Or third-party coordination services may emerge to help organize, coordinate, and collect research across providers (and potentially the pharmaceutical industry). Congress would need to keep these concerns in mind when finalizing the precise scope and details of this incentive.

Offering a tax credit to providers that generate information is important, but it won't necessarily solve either Problem. As Section II.C. showed, information must be organized, analyzed, and disseminated. Any tax credit should therefore be conditioned on some kind of dissemination. One method might be to mandate that providers register and publish all results on clinicaltrials.gov, a measure that currently isn't required for observational studies.[298] Congress might also consider requiring providers to publish any results, even if they show that a drug is not effective, in a format that would normally be sufficient to satisfy peer-reviewed journals.[299] Another option is to require providers to submit raw data and information, including study design and protocols, patient notes, etcetera, to the FDA for purposes of detailed evaluation for,

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[297] *See* Eisenberg & Price, *supra* note 44, at 29–30 (noting that payors have best practices and guidelines).

[298] In 1997, Congress enacted the Food and Drug Administration Modernization Act, which required IND applications for experimental treatments of serious and life-threatening diseases trials to register with the NIH. *See generally* Food and Drug Administration Modernization Act of 1997, Pub. L. No. 105-115, 111 Stat. 2296. Ten years later, Congress passed the FDAAA, which expanded the clinical trials required to register and expanded reporting requirements for results. *See generally* Food and Drug Amendments Act of 2007, Pub. L. No. 110-85, 121 Stat. 823 (2007). In 2000, the NIH, working with the FDA, launched clinicaltrials.gov to serve as the central registry. *See History, Policies, and Laws*, CLINICALTRIALS.GOV, https://clinicaltrials.gov/ct2/about-site/history (last visited Apr. 26, 2022). Currently federal regulations require only some clinical trials to be registered. *See* 42 C.F.R. § 11.60 (2020) (listing requirements of voluntary registration); *id.* § 11.62 (stating conditions under which mandatory registration is required). Specifically, only drugs in controlled trials require registration. *See id.* at § 11.60(a) (specifying that this section applies "[i]f a responsible party voluntarily submits clinical trial information for a clinical trial"). This excludes small feasibility studies and observational studies. *See* 42 C.F.R. § 11.22(b)(1)(ii) (2020). Under my proposals, providers undertaking these studies will be required to register and publish in clinicaltrials.gov. The penalties for failing to register would be substantial.

[299] In many cases, this never happens. *See e.g.*, Joseph S. Ross, Tony Tse, Deborah A. Zarin, Hui Xu, Lei Zhou & Harlan M. Krumholz, *Publication of NIH Funded Trials Registered in ClinicalTrials.gov: Cross Sectional Analysis*, 344 BMJ d7292 (2012). If trials are discontinued because of safety or efficacy concerns, it is critically important to make this information publicly available in a central repository.

among other things, safety and quality checks. Some centralized database or repository of this information would be critical.[300]

Using tax credits this way may be particularly effective because it ties them directly to outputs.[301] Unlike tax credits to pharmaceutical companies, tax credits to providers will produce *something*. That something, of course, may show nothing; the results may be inconclusive or may show that the drug has no known therapeutic effects. But even if the something is about nothing, *knowing* something about nothing is better than not knowing about anything at all. There's no risk that providers, unlike pharmaceutical firms, will bury results showing that a drug is not safe and effective because they don't have strong incentives to do so. Quite the opposite, to claim the tax credit, they *must* disseminate their data.[302]

Tax credits may be an attractive choice because they are more efficient than other push incentives, such as a government grant, for two reasons. First, administrative costs can be lower.[303] The government doesn't have to make allocation or investment decisions based on little or no information about the *known* safety and

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[300] While not all information can be public, making as much public as possible is likely to stimulate private industry to use it. This is already happening in other contexts, such as drug reimbursement and FDA regulation. *Compare* Simon, Off-Label Information, *supra* note 67, at 21–23 (describing drug compendia), *with* REDICA SYS. (FORMERLY GOVZILLA), https://govzilla.com/ (last visited Apr. 26, 2022) (providing a fee-for-service searchable database of FDA data on inspections, enforcement, and registration), DEFINITIVE HEALTH CARE, https://go.definitivehc.com/ (last visited Apr. 26, 2022) (collecting and publishing public information from the FDA), *and* FIRST DATABANK, https://www.fdbhealth.com/ (last visited Apr. 26, 2022) (collecting and publishing a variety of government statistics).

[301] *See* Hemel & Ouellette, *supra* note 277, at 326 ("[T]he most important question is not whether tax credits increase R&D inputs (i.e., spending), but whether tax credits increase R&D outputs (i.e., innovation).").

[302] They also may have an obligation to disclose safety risks they identify both to patients and to the doctors who treat them. *See*, *e.g.*, Kinetic Co. v. Medtronic, Inc., 672 F. Supp. 2d 933, 943 (D. Minn. 2009) (noting that once the hospital and physicians became aware of a risk posed by a device, they had an obligation to replace the product to avoid further injury caused by manufacturer). Pharmaceutical companies also have duties to disclose information, which can result in a purposeful failure to generate it. *See* Daniel R. Cahoy, *Medical Product Information Incentives and the Transparency Paradox*, 82 IND. L.J. 623, 628–29 (2007) (describing ex ante and ex post incentives to produce and disclose information).

[303] *See* Hemel and Ouellette, *supra* note 277, at 364–66 (noting "there is no evidence to support the claim that the administrative and compliance costs associated with R&D tax incentives are any greater than those associated with other innovative policy tools").

efficacy, as well as the *unknown* (or now well-known) risks, of the thousands of off-label uses.[304] The private market will. Second, this makes the tax credit efficient from another perspective: providers are likely to know their competences and capacities better than the government. Each provider can assess the value of research that qualifies for the tax credit. Providers with the best capabilities—those that have the infrastructure and know-how to conduct this research—are the most likely to avail themselves of the tax credit.[305]

None of this is meant to suggest that (non-refundable) tax credits should be preferred over grants or other subsidies in every case. Grants and subsidies have their own advantages, including an ability to shape research in a more nuanced and directed way. Grants (or refundable tax credits) also may provide a greater incentive for for-profit providers than for tax-exempt and not-for-profit providers. Not-for-profit hospitals, for example, may derive little or no benefit from a non-refundable tax credit because they have no tax liability.[306] In such cases, grants may be a more effective means for inducing providers to engage in clinical trials despite their higher administration costs.

Tax credits, though, do offer some unique advantages for for-profit providers that seek to engage in large-scale information generation efforts. And they have a proven record of inducing some R&D activity in the pharmaceutical space.[307] Given that nearly half of all physicians work for small, for-profit providers (small practices or as solo practitioners), it's also worth exploring how tax incentives might induce them to engage in observational studies and pragmatic clinical trials. Regardless of whether tax incentives are aimed at large providers, small providers, or both, they must be responsive to the financial pressures and structures of the providers that they aim to influence. Further research into the financial

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[304] In some cases, risks will be known based on existing research.

[305] Because of this, the tax credit may not be as effective as a direct subsidy, which might entice even the uninitiated providers to seek payment. Alternatively, a tax credit could be structured on a sliding scale designed to provide the greatest benefit (e.g., refundable tax credits) to those least likely to utilize the credit because of resource limitations. *See* Johnson, *supra* note 95, at 98 (noting that larger academic medical centers may be able to outpace smaller ones because they can build in bigger margins to grants and research activities).

[306] *See* 26 U.S.C. § 501(c)(3) (exempting nonprofit organizations from taxes if they meet certain requirements).

[307] *See supra* notes 277, 281.

structure and compensation models of these providers is therefore needed before recommending specific tax incentives.

E. MODIFIED MARKET EXCLUSIVITY, ROYALTIES, AND SUA SPONTE LABEL EXPANSIONS

Push incentives, discussed above, are the most natural fit because providers aren't structured to take advantage of the traditional pull incentives, such as regulatory exclusivity and patent law. But it may be possible to harness a version of regulatory exclusivity to stimulate more research. Doing so, however, would require changes to how the FDA approves supplemental indications.[308]

Currently drug approval—both for a new drug (which requires an NDA) and a new use (which requires an sNDA)—requires filing an application.[309] While it is conceivable that multiple providers might collaborate in research necessary to obtain FDA approval, they have little financial incentive to do so. FDA approval, of course, is beneficial because it signals a use's safety and efficacy. This is good for patients and physicians. Medicare uses this signal for payment decisions, reimbursing for almost all approved uses of approved drugs.[310] This is good for drug companies. For new uses, FDA approval entails regulatory (data) exclusivity.[311] This could be

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[308] Most literature on off-label uses assumes that the proper endpoint for research is FDA approval. *See, e.g.*, Dr. Bobbie Ann Mount, *in* NCATS Meeting, *supra* note 30, at 10 ("In an ideal world, we would like to solve the problems that exist between somebody coming up with a new idea for a therapeutic indication pair and actually getting that indication on a drug label."). It is not entirely clear that this is necessary or even desirable. Given the existing profile of many off-label uses, the FDA review may not be necessary for determining whether a drug is safe and effective. Or, if it is, it may be better to off-load that process to a private entity already doing this work. *See* Simon, *Off-Label Information*, *supra* note 67, at 19. *See* Kevin W. Su, Cary P. Gross, Nicholas S. Downing, Kerin B. Adelson & Joseph S. Ross, *Cancer Therapeutic Clinical Trials Supporting FDA Approval and Compendia Inclusion*, 9 AM. J. PHARM. BENEFITS 122, 127–28 (2017) (noting that evidentiary standards that compendia used for addition of off-label uses in cancer matched the one used by the FDA to approve supplemental indications).

[309] A drug sponsor may file either an NDA or an sNDA for a new use of a previously approved NDA. *See* 21 C.F.R. § 314.71 (2020).

[310] *See* 42 U.S.C. § 1395w-104(b)(3)(G)(iv) (Medicare Part D); Rachel E. Sachs, *Delinking Reimbursement*, 102 MINN. L. REV. 2307, 2314–15 (2018) (discussing Medicare Part B).

[311] *See supra* note 140.

good for drug companies but is of little use to providers because they usually have no ownership interest in the relevant drug (company).

One way to nudge providers to file applications is by modifying regulatory exclusivity. Instead of offering providers regulatory (data) exclusivity, which has little economic value, the government can provide them with a small royalty payment if their research is used to support an approved new use. In the same way a lottery attracts a large volume of players that are guaranteed to lose, this system might induce providers to (conduct and) publish their studies even when the chance of winning, and the amount to be won, is minute. Unlike a lottery, though, winners are paid, in part, for the quality of their efforts, not merely for their payment to play.

Payouts could be made according to an endless variety of formulae. One might calculate a fixed royalty per new use approved based on a percentage of the retail price of the drug. Another might leave the rate up to an administrative tribunal at the FDA or some other administrative agency within the department of Health and Human Services (the HHS), as occurs in other areas of law.[312] Whatever the approach, the rate should be small enough to only marginally increase drug prices and large enough to provide a modest inducement to providers to engage in research.[313] Royalties would be paid to providers only if they make *all* of their data publicly accessible.[314] A provider who seeks to participate in the royalty scheme, in other words, must make all of its data available to the public.

Providers would be entitled to an amount proportionate to their research contribution used for FDA approval. More robust studies would entitle providers who conducted them to a greater share of the royalty than providers who conducted smaller, uncontrolled

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[312] If a fixed royalty rate increases investment in more profitable uses at the expense of less profitable ones, the royalty-setting entity should have the flexibility to alter royalty rates to change incentives. One possibility is to have the GAO evaluate royalty effects and make recommendations to the FDA at regular intervals (e.g., every five years). Some government agencies already do this. *See* 17 U.S.C. § 801 (explaining that the copyright royalty board sets rates and reasonable terms for royalty payments).

[313] Another possibility is to direct all royalties to a fund that is managed by a board or trustee on behalf of all participating providers. The board or trustee would make decisions about how to allocate the funds it receives from royalty payments.

[314] Universal formatting issues are less of a problem here because standard protocols on clinical trials exist. *See supra* note 248 and accompanying text.

studies.[315] The FDA or the CMS could leverage existing evidence-rating systems to evaluate the quality of any given study and assign it weight for purposes of the royalty payment.[316]

A royalty might encourage providers to collaboratively research new uses and file NDAs for them. But it's not clear that the returns will be sufficiently high to encourage collaboration because the FDA approval process is expensive and because it will be difficult to exclude others from the new uses, reducing or eliminating the ability to charge supracompetitive prices. One alternative approach would be to use this incentive system but change the drug approval process. Rather than require applications for every new use, the FDA could consider and expand drug uses either by petition or sua sponte.

A petition approach, which the FDA uses for a variety of matters including drug approval,[317] would allow interested entities to lobby the FDA to consider expanding a drug's labeling.[318] Upon reaching some threshold—a certain quality of information or a certain number of petitions, for example—the FDA could voluntarily initiate a review for the expanded indication. The FDA would then have either the option or the obligation (if some threshold was met) to consider expanding the labeling to cover the new use in question. It could then solicit further comments and information from interested parties and conduct its own evaluation of existing evidence.

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[315] This could be implemented in various ways. One method would be to use the studies cited on the approved drug labeling. Another might be for the FDA to use internal scoring systems to quantify what role that the study played in approval of the new use.

[316] For some general background on different rating systems, see Simon, *Off-Label Information*, *supra* note 67, at 27–29.

[317] Regulations currently allow citizens to petition the FDA to take "administrative action." *See* 21 C.F.R. §§ 10.25, 10.30 (2020). A similar process could be used for providers seeking modified market exclusivity rights. The definition is broad enough to include label expansions. *See id.* § 10.3 ("Administrative action includes every act, including the refusal or failure to act, involved in the administration of any law by the Commissioner . . . ."); *see also* Michael A. Carrier & Daryl Wander, *Citizen Petitions: An Empirical Study*, 34 CARDOZO L. REV. 249, 259–63 (2012) (explaining citizen petitions and how companies can use them in anticompetitive ways by, for example, delaying generic and brand-name competitor entry).

[318] Citizens can file a petition specifically seeking to delay an ANDA, a 502(b)(2) drug application (a "paper" NDA), or NDA. *See* 21 C.F.R. § 10.31(a)(1). For example, petitions can be used to request withdrawal of guidance documents. *See* 21 C.F.R. § 10.115(f)(4).

Alternatively, the FDA could consider labeling updates sua sponte, something it has begun doing with certain cancer drugs,[319] and something it could do for other drugs under recently introduced legislation.[320] The FDA's current program could serve as a test case for a future in which the FDA "approves" new uses on its own initiative.[321] In this universe, the FDA would need to continually evaluate data on off-label uses as information becomes available. This approach would make good sense if other incentives designed to increase data about off-label uses—like those discussed above—were successful.[322] If chosen, this path would require a more systematic approach to evaluating new efficacy indications, including a detailed framework for initiating a review, reviewing, and eventually expanding indications.

One version of this could include an FDA-initiated notice-and-comment period. During this period, the FDA would solicit

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[319] Currently the FDA is updating labeling for oncology drugs in a somewhat related way through Project Renewal. *See Project Renewal*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/about-fda/oncology-center-excellence/project-renewal (last visited Apr. 26, 2022). The details of this project are quite scanty, but there are two goals. The first is to update labeling that is not consistent with the current standards in 42 C.F.R. § 201.56. The second is to assess labeling for drugs with "significant off-label use in" oncology. *See Project Renewal FAQ*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/about-fda/project-renewal/project-renewal-faq (last visited Apr. 26, 2021).

[320] Representatives Brett Guthrie and Doris O. Matsui recently introduced legislation that proposed to do something similar for previously-FDA approved drugs that had been withdrawn and were not covered by a patent or regulatory exclusivity. *See* Making Objective Drug Evidence Revisions for New Labeling Act of 2020, H.R. 5668, 116th Cong. (2d Sess. 2020).

[321] Under the Sentinel Initiative, the FDA has evaluated a number of drugs for safety concerns on its own. It also has, in limited cases, used non-traditional evidence to approve an NDA. *See* FDA RWE FRAMEWORK, *supra* note 160, at 9 ("In limited instances, FDA has accepted RWE to support drug product approvals, primarily in the setting of oncology and rare diseases."); Tony Durmowicz & Mike Pacanowski, *Novel Approach Allows Expansion of Indication for Cystic Fibrosis Drug*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/drugs/news-events-human-drugs/novel-approach-allows-expansion-indication-cystic-fibrosis-drug (last visited Apr. 26, 2022) ("To approve the indication expansion, a novel approach was used that relied on evidence from laboratory-based in vitro assay data."); Sandra Levy, *FDA Approves Expanded Indication for Amarin's Vascepa*, DRUG STORE NEWS, https://drugstorenews.com/fda-approves-expanded-indication-amarins-vascepa (last visited Apr. 26, 2022) (summarizing the FDA's approval of Amarin).

[322] When Congress enacted the 21st Century Cures Act, it provided that this kind of evidence could be used to support an NDA. *See* 21st Century Cures Act, H.R. 34, 114th Cong. (2016).

information about the safety and efficacy of a new indication that it's considering.[323] After obtaining public comment, the FDA could issue a new label if the evidence merited an update. Another might build on the recent legislation the House of Representatives passed (the MODERN Labeling Act).[324] The legislation, while specific to a narrow set of potential new uses,[325] authorized the Secretary of HHS to identify drugs whose labels merited updating based on several criteria.[326] The Secretary could identify drugs by entering into agreements with third parties to review evidence, by soliciting public input by holding public meetings, by soliciting public comments, or by "other means, as the Secretary determines appropriate."[327]

Either approach—petition or sua sponte—would give various organizations (patient rights advocates, consumer groups, pharmaceutical companies, and providers) the ability to seek expanded indications based on safety and efficacy data. With a formal petitioning process, this is obvious. But even with no official petitioning process, various stakeholders can pressure the FDA to study expanded indications—much in the same way groups petition the FDA for compassionate use.[328] It may even incentivize providers to collaborate on observational studies and pragmatic or clinical trials so that information could be packaged to the FDA in the most persuasive and coherent format.

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[323] For potential problems with notice-and-comment rulemaking, see for example, Richard Murphy, *Enhancing the Role of Public Interest Organizations in Rulemaking via Pre-Notice Transparency*, 47 WAKE FOREST L. REV. 681, 687–88 (2012).

[324] *See* Making Objective Drug Evidence Revisions for New Labeling Act of 2020, H.R. 5668, 116th Cong. (2d Sess. 2020) (discussing the legislation).

[325] The legislation defined "covered drug" as one with no existing patent or regulatory exclusivity protections and whose prior FDA approval had been withdrawn for reasons unrelated to safety or effectiveness. *See* Making Objective Drug Evidence Revisions for New Labeling Act of 2020, H.R. 5668, 116th Cong. § (a)(1)(A)–(B) (2d Sess. 2020).

[326] *See* Making Objective Drug Evidence Revisions for New Labeling Act of 2020, H.R. 5668, 116th Cong. § 2(a)(1)(A)–(C) (2d Sess. 2020) (defining "covered drug"); *id.* § 2(b) (authorizing HHS Secretary to identify drugs for labeling updates).

[327] *Id.* § 2(b)(1)–(2).

[328] *See Expanded Access*, *supra* note 46. Activists during the HIV/AIDS epidemic were crucial to moving the FDA toward the current expanded access paradigm. *See also* E. Nichols, *Historical Perspective – Expanding Access to Investigational Therapies for HIV Infection and AIDS*, NCBI BOOKSHELF (1991), https://www.ncbi.nlm.nih.gov/books/NBK234129/ (emphasizing the historical background of the expanded access program).

This kind of system is not without risk. One principal worry is that the system will perpetuate the shortcomings of the existing private market—namely, providers will engage in research that pays the highest return, or the quickest one.[329] This could mean investing in research in drugs most likely to obtain approval (based on previous research) or those that generate the most sales. In either case, the system would bend toward maximizing the reward rather than patient benefit.

While this is a real problem, it is not insurmountable. Royalties or payments could be structured to reflect need instead of, or in addition to, sales. Alternatively, a fixed fee—or a prize[330]—could be used to reduce some of the distortionary effects of profit-seeking that occur in the current pharmaceutical market. Prizes—rewards for achieving a goal set by the government—could also be tied to various socially desirable outcomes, such as approval of a new indication for treatment of a rare disease or of a widespread disease with limited or no treatments. The size of the prize could be determined by studying the likely social benefit from obtaining the desired information.[331]

Attention to rewards should not obscure the positive externalities of generating negative information. Providers that engage in information generation that shows a drug *is not* safe or effective have done something socially beneficial. That particular off-label use can be ruled out, saving the costs of the medication, any potential costs of adverse events, and potentially, an improved patient outcome with alternative or no treatment. To ensure that there are adequate incentives to invest in trials that may produce such information, any rewards system should account for the positive externalities of negative information. To do so, it's important that any royalty or reward system is coupled with incentives like those discussed in Sections A–C and potentially

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[329] *See* Budish et al., *supra* note 26, at 2045–46. (noting that "corporate short-termism and fixed patent terms reinforce each other in distorting private research dollars away from long-term investments").

[330] Rachel E. Sachs, Paul B. Ginsburg & Dana P. Goldman, *Encouraging New Uses for Old Drugs*, 318 JAMA 2421, 2422 (2017) ("The government or foundations could provide prizes or financial incentives to payers, health care systems, or manufacturers for conducting new-use research.").

[331] *See* Sachs et al., *supra* note 330, at 2422 ("The reward amount could be tied to a useful clinical and policy end point, such as reduced nursing home admissions.").

others not yet known. This is particularly important for providers because they, along with payers, are one of the few entities that has a direct interest—improving patient outcomes[332]—in producing negative information about drugs that might be harmful or useless.[333]

V. CONCLUSION

This Article has argued that two of medicine's pressing problems—doctors prescribing approved drugs for unapproved uses and firms lacking incentives to develop new uses of existing drugs—often arise from the same informational deficit: a lack of safety and efficacy information about the unapproved uses of approved drugs, so-called off-label uses. It pointed out that all new uses of approved drugs are off-label uses, and some off-label uses are new. Safety and efficacy information about new uses, in other words, will always be safety and efficacy information about off-label uses. And some information about off-label uses will be information about new uses.

This observation revealed a new possible solution to both of these tricky Problems: incentivize those entities that already produce, or have the capability to produce, this information to collect, organize, and disseminate it. Healthcare providers, it was noted, not only have this capability but also have a variety of institutional competencies and advantages that make them a rich potential source of the needed information. To show how these provider-oriented inducements might function, this Article adapted four incentives from the existing innovation literature: two subsidies, a tax credit, and a royalty or a prize. Each of these examples

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[332] Providers may have countervailing financial interests if they are compensated based on (service) volume. More prescriptions may lead to larger payments. And more adverse events from off-label prescriptions, for example, may increase the overall profit margin of a provider. But providers also have ethical and legal obligations when they treat patients that limit the influence of these potentially socially undesirable economic incentives. *See* Frank A. Riddick, Jr., *The Code of Medical Ethics of the American Medical Association*, 5 OCHSNER J. 6, 5–7 (2003). Doctors certainly don't set out to cause adverse events, and the primary aim of treatment isn't to inflate provider costs.

[333] Eisenberg & Price, *supra* note 44, at 5 ("Studying the consequences of past clinical care to improve healthcare practice is an important research frontier with the potential to yield valuable innovations.").

illustrated that there are ways to leverage provider capabilities to help solve both of these important problems.

What this Article did not do—and what future work should do—was explore all possible incentives that could be applied to providers and their advantages and disadvantages. This would have required a more detailed analysis of providers and their current institutional operations and infrastructure. Prizes, for example, might be useful to generate data on off-label uses—even if those data are negative. But a particular type of prize may work well for large but not small providers, or vice versa, because of economic and resource constraints or specialization. Beyond the specific setting in which prizes may be used, as an incentive they are less effective when the social value of the desired activity is difficult to estimate. Similar analysis applies to non-refundable tax credits. While they work well for pharmaceutical companies, they may not work for providers like hospitals, many of which are non-profit entities. In such cases, a direct cash payment—a grant or refundable tax credit—might do more to induce providers to maintain systems that collect, organize, and disseminate information about off-label uses, particularly if grants are made more than once. In other words, each type of incentive has its own benefits and drawbacks that need to be assessed relative to the social problems they are designed to address and the entities to which they apply. These issues, and many others, should be addressed in future research.