Gatekeeping Drugs

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How much evidence should pharmaceutical manufacturers be required to provide before they can market new drugs? With drug costs ballooning to over $500 million and marketing approval decisions increasingly contested, scholars have reached two conflicting views. Public-health scholars tend to think high evidentiary standards overseen by a strong governmental gatekeeper are important to medical progress and protecting consumers, while pro-market scholars view them as impediments to innovation and a threat to public health. This Article shows these seemingly diametrically opposed views can be married using an existing system that reimburses certain unapproved uses of approved drugs—so-called "off-label" uses—based on evidence that they work. In these cases, reimbursement acts like an initial gatekeeper with respect to certain unapproved uses by "approving" them through payment. This system of off-label approval, therefore, resembles one that pro-market scholars desire: drug approval regulates drug entry to the market and reimbursement regulates (unapproved) drug use once on the market. Extending this system across all drug regulation reveals that changing drug approval standards has benefits and costs that both pro-market and public-health scholars have not fully considered. It demonstrates that the potential benefits of changing drug approval are difficult to predict given the costs imposed by significantly disrupting the existing drug

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ecosystem. This suggests reform to drug approval should be methodical, carefully controlled, and measured.

INTRODUCTION

Drug prices are soaring. The median annual list price for a new drug in 2023 was $300,000.[1] In the United States alone, Americans spent over $600 billion in 2022, an amount that is projected to increase to $1.5 trillion within the next five years.[2] Part of that price tag reflects the cost of developing enough evidence to satisfy government regulators that a drug is safe and effective, which can exceed $1 billion for a new drug.[3] High development costs and evidentiary standards also restrict the supply of drugs that reach the market. A cancer patient dies while a drug that may have helped her languishes on the shelf of a pharmaceutical lab. A patient with severe, intractable nerve pain lives in agony without access to a drug that has shown promise but has stalled in regulatory review. Just how many pharmaceutical innovations are lost or delayed, and how much is spent as a result, because a powerful gatekeeper—the Food and Drug Administration ("FDA")—says there is not enough evidence to allow consumers access to them?[4]

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1. Deena Beasley, *Prices for New US Drugs Rose 35% in 2023, More Than the Previous Year*, REUTERS (Feb. 23, 2024), https://www.reuters.com/business/healthcare-pharmaceuticals/prices-new-us-drugs-rose-35-2023-more-than-previous-year-2024-02-23 [https://perma.cc/M5FK-XMTG].

2. Eric M. Tichy et al., *National Trends in Prescription Drug Expenditures and Projections for 2023*, 80 AM. J. HEALTH-SYS. PHARM. 899, 900 (2023); Press Release, Evaluate, Evaluate Forecasts Global Pharmaceutical Market to Be Worth $1.6tn in 2028 (Aug. 15, 2023), https://www.evaluate.com/press_release/evaluate-forecasts-global-pharmaceutical-market-to-be-worth-1-6tn-in-2028 [https://perma.cc/4YEZ-PZEP].

3. Joseph A. DiMasi et al., *The Price of Innovation: New Estimates of Drug Development Costs*, 22 J. HEALTH ECON. 151, 181 (2003).

4. A recent boom in innovation scholarship has tended to focus on incentives other than, or in addition to, FDA approval. *See generally, e.g.*, Daniel J. Hemel & Lisa Larrimore Ouellette, *Valuing Medical Innovation*, 75 STAN. L. REV. 517 (2023) [hereinafter Hemel & Ouellette, *Valuing Medical Innovation*]; W. Nicholson Price II, *The Cost of Novelty*, 120 COLUM. L. REV. 769 (2020); Daniel J. Hemel & Lisa Larrimore Ouellette, *Innovation Policy Pluralism*, 128 YALE L.J. 544 (2018); Benjamin N. Roin, *Intellectual Property Versus Prizes: Reframing the Debate*, 81 U. CHI. L. REV. 999 (2014); Benjamin N. Roin, *The Case for Tailoring Patent Awards Based on Time-to-Market*, 61 UCLA L. REV. 672 (2013); Benjamin N. Roin, *Unpatentable Drugs and the Standards of Patentability*, 87 TEX. L. REV. 503 (2008); W. Nicholson Price II, *Grants*, 34 BERKELEY TECH. L.J. 1 (2019); JAMES BESSEN & MICHAEL J. MEURER, PATENT FAILURE: HOW JUDGES, BUREAUCRATS, AND LAWYERS PUT INNOVATORS AT RISK (2009); Robin Feldman, *Regulatory Property: The New IP*, 40 COLUM. J.L. & ARTS 53 (2016). Scholars have also thought about FDA's role in innovation policy. *See, e.g.*, Rachel E. Sachs et al., *Rethinking Innovation at FDA*, 104 B.U. L. REV. 513 (2024); Amy Kapczynski, *Dangerous Times: The FDA's Role in Information Production, Past and Future*, 102 MINN. L. REV. 2357 (2018); Rebecca S. Eisenberg, *The Role of the FDA in Innovation Policy*, 13 MICH. TELECOMM. & TECH. L. REV. 345 (2007).

Some pro-market[5] scholars—like Professors Henry Miller, Richard Epstein, Sam Peltzman, and Daniel Klein—think the answer is "a lot." They have argued that the government's gatekeeping role is a history of "pernicious,"[6] "relentless expansion of administrative responsibility"[7] and a "disaster"[8] that has caused "enormous harm to the health of the American public."[9] Since the government's expansive gatekeeping has provided "little or no additional protection of public health,"[10] some conclude that "too many resources have been devoted to testing . . . drug safety and efficacy before marketing,"[11] while others argue more forcefully that "the longstanding banned-till-permitted [gatekeeping] policies" should be discarded because they "have no market-failure rationale."[12] Although the last position is an outlier, some pro-market scholars claim that limiting the government's gatekeeping role to ensuring drugs are safe—rather than safe *and effective*—would improve innovations in drug development, enable quicker patient access, and reduce drug prices.[13]

Other, typically public health-oriented, scholars disagree.[14] They argue that liberalizing drug approval strips the gatekeeper of its primary means of

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5. The term "pro-market" is an imperfect descriptor. Some scholars in this group, for example, strongly disfavor governmental intervention and may appropriately be described as "libertarian." But others may argue that the current system vests too much regulatory authority in a government agency or limits (too aggressively) the working of the free market. These scholars are more accurately characterized as falling within the pro-market tradition than the narrower libertarian one. To capture these and other views, this Article refers to these scholars as "pro-market."

6. Henry I. Miller, *Failed FDA Reform*, REGULATION, Summer 1998, at 24, 24.

7. RICHARD ALLEN EPSTEIN, OVERDOSE: HOW EXCESSIVE GOVERNMENT REGULATION STIFLES PHARMACEUTICAL INNOVATION 10 (2006).

8. Sam Peltzman, *Regulation and the Natural Progress of Opulence*, ECON. AFFS., June 2010, at 33, 38.

9. Daniel B. Klein, *Economists Against the FDA: The Quack Platitudes That Drive Public Policy Are Dead*, FOUND. ECON. EDU. (Sept. 1, 2000), https://fee.org/articles/economists-against-the-fda [https://perma.cc/6WG8-HFT9] (quoting Milton Friedman in DURK PEARSON & SANDY SHAW, FREEDOM OF INFORMED CHOICE: FDA VERSUS NUTRIENT SUPPLEMENTS 39 (1994); *see also* Lacy Glenn Thomas, *Regulation and Firm Size: FDA Impacts on Innovation*, 21 RAND J. ECONS. 497, 513 (1990) (showing that FDA regulations are especially harmful to smaller firms and tend to benefit larger firms by reducing competition).

10. Miller, *supra* note 6, at 25.

11. SAM PELTZMAN, REGULATION OF PHARMACEUTICAL INNOVATION 83 (1974).

12. Daniel B. Klein, *Colleagues, Where Is the Market Failure? Economists on the FDA*, 5 ECON. J. WATCH 316, 330 (2008).

13. *See* PELTZMAN, *supra* note 11, at 9.

14. Like with the term "pro-market," the term "public health" does not perfectly describe every scholar who subscribes to this critique. The label is nevertheless useful because it describes a central motivating concern that simultaneously unites these scholars and distinguishes them from pro-market ones.

ensuring medical innovations are safe and effective: the government's ability to demand information and further studies before allowing market access.[15] To the contrary, they contend that the government's gatekeeping power ought to be enlarged or at least maintained, rather than reduced, because FDA has increasingly allowed drugs on the market with insufficient evidence that they are safe and effective.[16] These scholars argue that in such a system, government intervention can reduce drug costs to consumers in other ways, such as through price negotiation, with a tolerable drop in innovation—indeed, strong approval standards are an important tool to drive and maintain the very innovation that commands higher prices.[17]

Yet there is a commonality in the seemingly conflicting debate about the optimal role of this gatekeeper: both pro-market and public health-oriented scholars tend to treat FDA as the primary sluice in the pathway to market.[18]

But imagine a different system, where the FDA is not the only gatekeeper of drugs but simply the initial one. In such a system, the FDA would approve drugs mainly based on a low evidentiary bar (i.e., evidence of "safety"), increasing the effects desired by pro-market scholars. And insurers, led by the federal government, would pay for drug uses based on a higher

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15. *See, e.g.*, Kapczynski, *supra* note 4, at 2358–59.

16. *See* Vinay Prasad et al., *Low-Value Approvals and High Prices Might Incentivize Ineffective Drug Development*, 15 NATURE REVS. CLINICAL ONCOLOGY 399, 400 (2018); Nicholas S. Downing et al., *Clinical Trial Evidence Supporting FDA Approval of Novel Therapeutic Agents, 2005–2012*, 311 JAMA 368, 369 (2014); John Wilkerson, *ALS Patients Support Bill That Could Help Patients with Other Rare Diseases*, STAT (Oct. 26, 2023), https://www.statnews.com/2023/10/26/als-patients-support-bill-that-could-help-patients-with-other-rare-diseases [https://perma.cc/2US9-MLLR]; Kapczynski, *supra* note 4, at 2379; *Unlocking Hope: Access to Therapies for People with Rare, Progressive, and Serious Diseases Before the S. Special Comm. On Aging*, 118th Cong. 13–15 (2023) (statement of Holly Fernandez Lynch, Assistant Professor, University of Pennsylvania).

17. Christopher P. Adams, *CBO's Simulation Model of New Drug Development* 1 (Cong. Budget Off., Working Paper No. 2021-09, 2021), https://www.cbo.gov/system/files/2021-08/57010-New-Drug-Development.pdf [https://perma.cc/7F3K-LXFA]. CBO estimates that the 'Lower Drug Costs Now Act' will decrease different types of clinical trials by several percentage points. *See id.* at 22–24. There are also proposals that blend elements of both camps, attempting to reduce time to market by eliminating certain requirements but keeping the majority intact. *See, e.g.*, Mark A. Kassel, *Getting There First with the Best: The Need to Shorten the Prescription Drug Approval Process*, 27 VAL. U. L. REV. 95, 125 (1992).

18. This is not to suggest that scholars have ignored the role reimbursement can and does play in innovation—a subject that has blossomed into a significant body of work. *See, e.g.*, Mark A. Lemley et al., *The Medicare Innovation Subsidy*, 95 N.Y.U. L. REV. 75, 105–21 (2020); Rachel E. Sachs, *Prizing Insurance: Prescription Drug Insurance as Innovation Incentive*, 30 HARV. J.L. & TECH. 153, 178–92 (2016); Hemel & Ouellette, *Valuing Medical Innovation*, *supra* note 4, at 529. Rachel Sachs, for example, has suggested delinking FDA approval from reimbursement. *See* Rachel E. Sachs, *Delinking Reimbursement*, 102 MINN. L. REV. 2307, 2310 (2017). Critically, however, she would leave the strength of FDA's gatekeeping function intact. *Id.* at 2323.

evidentiary bar (i.e., evidence of "efficacy"), limiting the potential harmful consequences feared by public health-oriented scholars.[19] Here FDA would act as the gatekeeper of market *access* while insurers act as the gatekeeper of drug *use*.[20]

While the system may not seem either politically or practically viable, this Article shows that it already exists in one area of medicine: certain unapproved uses of approved drugs—so-called off-label uses.[21] When physicians prescribe a drug off-label, sometimes insurance companies must decide whether to pay for it based on evidence of efficacy.[22] Here the role of these two gatekeepers shifts, and FDA approval regulates drug *entry* to the market and reimbursement regulates (unapproved) drug *use* once on the market.[23] In evaluating whether to pay for drugs based on evidence that they work, insurance acts as the "Other FDA" with respect to certain off-label uses by "approving" them through payment.

While both public and private insurance companies perform this function, the most significant and influential actor is the federal agency that makes reimbursement decisions for public insurance: the Centers for Medicare & Medicaid Services ("CMS"). In particular, the public insurance program for the elderly and disabled, Medicare,[24] sets drug insurance policy for 53 million people and accounted for more than thirty percent of all drug spending in 2021.[25] CMS's coverage decisions, including for off-label uses, are extremely

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19. Casting drugs in terms of "safety versus efficacy" is somewhat confusing because the two concepts are inextricably intertwined. *See infra* Section II.B.

20. This is *not* the point that whether insurance pays for a drug can limit access—a point that has been made repeatedly. It is rather that in certain cases insurance can limit how the drug is used—a decision made based on evidence of efficacy. *See* Sachs, *supra* note 17, at 2321.

21. Another analog, though imperfect, is found in the European Union, where a centralized agency makes authorization (or approval) recommendations. Member states, however, decide whether to permit marketing and how to set reimbursement policies. *See* Commission Regulation 726/2004, 2004 O.J. (L 136) (EC) (as amended); Commission Regulation 2019/6, 2019 O.J. (L 4) (EU).

22. *Understanding Unapproved Use of Approved Drugs "Off Label,"* U.S. FOOD & DRUG ADMIN., https://www.fda.gov/patients/learn-about-expanded-access-and-other-treatment-options/understanding-unapproved-use-approved-drugs-label [https://perma.cc/JVT3-X6D4].

23. As noted in Section I.D., access is not *solely* determined by insurance. Patients may still cash pay for off-label uses that are prescribed but not covered. *See infra* Section I.D.

24. *See* 42 U.S.C. § 1395ff (describing Medicare Parts A and B); 42 U.S.C. § 1395w-22(g) (describing Medicare Part C); 42 U.S.C. § 1395w-104 (describing Medicare Part D).

25. *See, e.g.*, Juliette Cubanski, *A Current Snapshot of the Medicare Part D Prescription Drug Benefit*, KAISER FAM. FOUND. (Oct. 9, 2024), https://www.kff.org/medicare/issue-brief/a-current-snapshot-of-the-medicare-part-d-prescription-drug-benefit [https://perma.cc/L9ZL-8VXY]; Juliette Cabanski & Tricia Neuman, *A Small Number of Drugs Account for a Large Share of Medicare Part D Spending*, KAISER FAM. FOUND. (July 12, 2023),

influential. Most private insurers take cues from CMS's (rules for) coverage decisions,[26] and more than half of all states have passed laws mandating off-label insurance coverage frameworks for cancer drugs that mirror the one used by CMS.[27] While CMS will reimburse off-label uses, this gatekeeper, like FDA, has specific evidentiary criteria for determining whether to pay for them.[28] In effect, CMS acts as the "Other FDA" with respect to these off-label uses, "approving" them through reimbursement.

This Article uses the dual-gatekeeping insight to test pro-market scholars' proposals to reduce the power of the governmental gatekeeper.[29] In other words, it uses CMS's role as the Other FDA for certain off-label uses to test proposals to increase innovation and access by lowering or eliminating efficacy standards for drug approval. Using CMS instead of private payors has several advantages that make it useful, if not perfect, for both demonstrating the reconceptualization and articulating and testing pro-market proposals. First, it has a well-described public algorithm that applies to all decisions to cover and reimburse drugs. Second, certain features of this algorithm make it particularly illustrative, including its reliance on external evaluators of evidence and its requirement for information about off-label drug use in certain contexts. Third, it shows how public and private models may intersect since Medicare is overseen by the government but administered by private entities. Fourth, private companies and state laws tend to take cues from CMS coverage decisions on off-label use, making it a strong de facto (and sometimes de jure) regulator of certain unapproved uses of approved

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https://www.kff.org/medicare/issue-brief/a-small-number-of-drugs-account-for-a-large-share-of-medicare-part-d-spending [https://perma.cc/YCN4-PAPJ]; DEP'T OF HEALTH & HUM. SERVICES, OFF. SCI. & DATA POL'Y: TRENDS IN PRESCRIPTION DRUG SPENDING, 2016–2021, at 1 (2022), https://aspe.hhs.gov/sites/default/files/documents/88c547c976e915fc31fe2c6903ac0bc9/sdp-trends-prescription-drug-spending.pdf [https://perma.cc/FEX3-2Z39]. CMS also pays for prescription drug claims under Medicaid, which insures low-income individuals. *See* Juliette Cubanski et al., *How Does Prescription Drug Spending and Use Compare Across Large Employer Plans, Medicare Part D, and Medicaid?*, KAISER FAM. FOUND. (May 20, 2019), https://www.kff.org/medicare/issue-brief/how-does-prescription-drug-spending-and-use-compare-across-large-employer-plans-medicare-part-d-and-medicaid [https://perma.cc/7Q4Z-5YP].

26. *See* discussion *infra* Section I.A.

27. Fabrice Smieliauskas et al., *State Insurance Mandates and Off-Label Use of Chemotherapy*, 27 HEALTH ECONS. e55, e56 (2017); *see also* NAT'L ASS'N INS. COMM'RS, OFF-LABEL DRUG USE MODEL ACT, at ST-148-3 to -6 (1995), https://content.naic.org/sites/default/files/inline-files/MDL-148.pdf [https://perma.cc/CT7A-ZLUE] (listing states with such laws).

28. *Drugs and Biologicals, Coverage of, for Label and Off-Label Uses*, CTRS. FOR MEDICARE & MEDICAID SERVS., https://www.cms.gov/medicare-coverage-database/view/lcd.aspx?lcdid=39774&ver=4 [https://perma.cc/MWE6-GARK].

29. The limitations of using CMS to conduct this thought experiment are described *infra* Part III.

drugs. Finally, CMS is a governmental entity with newly imbued authority to evaluate the quality and kind of evidence when deciding whether to cover and reimburse specific drugs, making it potentially more amenable to implementation than relying on an entirely new regulatory entity or leaving efficacy decisions entirely to the private market.

By extending the use of a secondary gatekeeper focused on efficacy across all drug regulation, this Article makes two additional contributions. First, it shows that the divergent approaches of pro-market and public-health scholars can be married, if not perfectly, then conceptually. Second, and just as importantly, this Article demonstrates the potential costs and benefits of this new conceptual matrimony, which scholars from both camps have not fully appreciated. For example, a system that approves drugs based on safety and reimburses drugs based solely on the efficacy of the prescribed use would reduce unnecessary off-label prescribing and more accurately price drugs according to the evidence supporting their use. But it would also create costs, including disrupting drug advertising and liability regimes, which are currently predicated on FDA's efficacy evaluation. While a complete "net-benefit calculation" may be "chimerical,"[30] identifying the potential costs and benefits illustrates the significance and complexity of a seemingly simple change to the government's gatekeeping role. In short, this Article shows that changing drug approval standards is risky, disruptive, and of highly uncertain benefit.

This suggests that the most prudent way to regulate drugs is using a scientific approach, one which may need to be taken further than current FDA programs have anticipated. This could include a systematic and comprehensive study of the market and prescribing effects of the current system where CMS acts as the Other FDA and an analysis of private insurer behavior with respect to some or all off-label uses.[31]

This Article proceeds as follows. Part I explains a common way of thinking about drug approval, with FDA as the most important gatekeeper

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30. Klein, *supra* note 12, at 317.

31. For one example of how such study might proceed, see OFF. INSPECTOR GEN. & DEP'T HEALTH & HUM. SERVS., A-09-20-03033, MEDICARE PART D PLAN SPONSORS AND CMS DID NOT ENSURE THAT TRANSMUCOSAL IMMEDIATE-RELEASE FENTANYL DRUGS WERE DISPENSED ONLY TO BENEFICIARIES WHO HAD A CANCER DIAGNOSIS (Feb. 28, 2023), https://www.oversight.gov/sites/default/files/documents/reports/2023-04/92003033.pdf [https://perma.cc/FGU3-324J]. *See generally* Lisa Larrimore Ouellette, *Patent Experimentalism*, 101 VA. L. REV. 65, 114–18 (2015) (proposing a regulated framework for policy experimentation with regard to patents); Michael Abramowicz et al., *Randomizing Law*, 159 U. PA. L. REV. 929, 974–79 (2011) (discussing the benefits of randomized studies and recommending guidelines for legislatures and administrative agencies to initiate such studies).

determining how drugs are approved and used. It then shows that in cases involving certain off-label uses, FDA's primary gatekeeping function is to determine market access while insurers, notably CMS, serve as the gatekeeper of drug use by deciding which ones to pay for. This Part argues that in these cases CMS acts as an important secondary gatekeeper, a kind of Other FDA, by evaluating coverage and reimbursement decisions using evidence that the drug is safe and effective for a given use. It concludes with some caveats about the limits of this analogy, highlighting the differences in authority, processes, and impact between the primary gatekeeper, FDA, and a secondary one like CMS.

Part II explains economists' proposals to alter FDA approval to increase efficiency and situates this Article's proposal—to regulate safety through FDA approval and efficacy through CMS coverage and reimbursement—within them. It shows how they differ from each other and the status quo. It then evaluates whether separating safety and efficacy is conceptually possible. This Part concludes by identifying four core issues that must be addressed to implement the proposed regime.

Part III uses this proposal to examine whether this kind of system could apply to drug regulation generally. This Part identifies key costs and benefits associated with implementing the proposal that both pro-market and public-health scholars may not have anticipated. It explains that changing FDA requirements could have drastic effects on drug development, legal doctrines, and the behavior of actors affected by both, including physicians, patients, insurers, and manufacturers. This Part concludes by arguing that additional work and testing is needed to evaluate the costs and benefits of any modification to the existing system. The best way forward, in other words, is probably to move in small, methodical steps.

I. PRIMARY AND SECONDARY GATEKEEPING

This Part explains the common picture of drug approval with FDA as the primary gatekeeper of innovation, then shows how in cases of certain off-label uses, there are two gatekeepers rather than one. The first, FDA, regulates drug market *access* and the second, CMS, regulates drug *use*. Section I.A situates discussions of FDA's gatekeeping role and reimbursement in the context of innovation scholarship. Section I.B explains briefly why reimbursement is typically thought of as an innovation incentive but not a conventional drug regulator. Section I.C then shows how the seemingly imaginary system described in the introduction is a reality for certain off-label uses. In other words, it shows how in some cases payors like CMS take on an FDA-like role by deciding whether to pay for drugs based

on evidence of efficacy. Section I.D concludes by highlighting the conceptual, practical, and legal limitations of analogizing CMS to an initial gatekeeper like FDA.

A. One Gatekeeper, One Payor

The FDA's gatekeeping role is often conceptualized as a public safety watchdog. For the past seventy years, its role has been to protect public health by approving only those drugs that are safe and effective under specific conditions of use.[32] Scholars have added to this description by pointing out that FDA has other important functions: it generates safety and effectiveness data that might otherwise not exist,[33] reduces information costs and asymmetries,[34] makes choices that affect innovation incentives even when it does not mean to,[35] and influences investment decisions by exercising its authority to approve drugs.[36]

Within this picture, drug reimbursement has not gone unnoticed. Paying for drugs has always been viewed as one of several innovation incentives,[37] but only recently have legal scholars begun to explore specific innovation-related effects of reimbursement. A significant portion of this scholarship, however, assumes that the existing framework of drug approval is the relevant and appropriate baseline.[38] Proposals to change reimbursement are typically focused on either improving the FDA's gatekeeping function or at

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32. *See* Federal Food, Drug, and Cosmetic Act § 505, 21 U.S.C. § 355.

33. Eisenberg, *supra* note 4, at 370.

34. *See* Ariel Katz, *Pharmaceutical Lemons: Innovation and Regulation in the Drug Industry*, 14 MICH. TELECOMM. & TECH. L. REV. 1, 39–40 (2007). Primary gatekeeping reduces information costs and asymmetries for consumers (physicians and patients) by off-loading them to FDA. Of course, FDA reduces its own information asymmetry relative to firms by demanding information about drugs under review. *See* Mary K. Olson, *Firm Characteristics and the Speed of FDA Approval*, 6 J. ECONS. & MGMT. STRATEGY 377, 387 (1997); Daniel P. Carpenter, *The Political Economy of FDA Drug Review: Processing, Politics, And Lessons for Policy*, 23 HEALTH AFFS. 52, 53 (2004).

35. *See* Sachs et al., *supra* note 4, at 526–29.

36. *See* Carpenter, *supra* note 34, at 52. This is not an exclusive list.

37. For a review of push and pull incentives, see, for example, Hemel & Ouellette, *Valuing Medical Innovation*, *supra* note 4 (arguing that pharmaceutical-innovation push incentives focused on market exclusivity and government subsidized health programs are weak, and proposing a framework for value-based pull incentives); Adrian Towse & Priya Sharma, *Incentives for R&D for New Antimicrobial Drugs*, 18 INT'L J. ECON. BUS. 331, 334 (2011) ("[P]olicy developments in the EU and the US have shifted over time from an emphasis on conservation of existing antimicrobials to implementing incentives to create new ones.").

38. *See, e.g.*, Eisenberg, *supra* note 4, at 347–48.

least not reducing it.[39] This baseline often carries over into political proposals. For example, recently passed legislation designed to reduce drug prices focused on payment rather than approval.[40]

Despite the importance of reimbursement, it is often overshadowed by FDA's gatekeeping function. This is because FDA approval often translates to automatic—or near-automatic—coverage and reimbursement by CMS, one of the most important insurers in the market. CMS will cover and pay for drugs that are "reasonable and necessary" to treat, mitigate, or diagnose a disease or condition of a beneficiary.[41] What is reasonable and necessary depends on how drugs are administered and accessed.[42] When an FDA-approved drug is administered in a hospital or physician's office under Part

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39. The assumption is that efficacy requirements weed out worthless drugs, and the government or other entities can effectively price drugs to correspond to some other metric, such as "social value." *See infra* Section III.B; *see also* Hemel & Ouellette, *Valuing Medical Innovation*, *supra* note 4, at 517–18 ("[T]he United States pays high prices for drugs of limited efficacy, but those high prices fail to spur the development of more effective drugs in critical areas. To break out of this bind, the federal government should reward social value directly, using cost-effectiveness analysis to set the prices it pays for medical innovations without limiting patient access.").

40. *See, e.g.*, Inflation Reduction Act of 2022, Pub. L. No. 117-169, § 1194(e)(2), 136 Stat. 1818, 1843 (codified at 42 U.S.C. §1320f-3). Opponents, of course, have noted that reducing reimbursement for drugs may hinder innovation by causing some firms to refrain from developing therapeutics or seeking approval in the first place. *Inflation Reduction Act's Unintended Consequences*, PHRMA, https://phrma.org/en/Inflation-Reduction-Act [https://perma.cc/376W-JEY9].

41. 42 U.S.C. § 1395y. Until recently, CMS had rarely attempted to define "reasonable and necessary"—something it recently did, then repealed its definition. *See* Medicare Coverage of Innovative Technology (MCIT) and Definition of "Reasonable and Necessary," 86 Fed. Reg. 62944 (Nov. 15, 2021) (codified at 42 C.F.R. § 405).

42. Medicare has four parts: A (hospital insurance), B (outpatient), C (Medicare Advantage), and D (prescription drugs). *Parts of Medicare*, MEDICARE, https://www.medicare.gov/basics/get-started-with-medicare/medicare-basics/parts-of-medicare [https://perma.cc/ZG9U-EFK4]. This Article focuses only on Parts B and D.

B[43] and in accordance with its labeling, CMS will generally pay for the drug.[44] Thus, FDA approval typically is equivalent to guaranteed payment for a drug when administered in a physician's office or hospital and consistent with the labeling.[45] For prescription drugs that patients obtain at retail pharmacies under Part D,[46] CMS must cover at least two drugs in each therapeutic class.[47] Additionally, CMS covers "all or substantially all"[48] drugs in six "protected

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43. *See, e.g.*, CTRS. FOR MEDICARE & MEDICAID SERVS., MEDICARE CLAIMS PROCESSING MANUAL: CHAPTER 4—PART B HOSPITAL (2024), https://www.cms.gov/regulations-and-guidance/guidance/manuals/downloads/clm104c04.pdf [https://perma.cc/CT8Z-HGCJ] (providing billing guidance to hospitals and providers); Balanced Budget Act of 1997, Pub. L. No. 105-33, §§ 4556–4557, 111 Stat. 251, 462–64 (codified at 42 U.S.C. § 1395u(o)(1)(C)). Medicare pays for most Part B covered drugs based on the average sales price (ASP) plus a six percent add-on. MEDICARE PAYMENT ADVISORY COMM'N, REPORT TO THE CONGRESS: MEDICARE AND THE HEALTH CARE DELIVERY SYSTEM 109, https://www.medpac.gov/wp-content/uploads/import_data/scrape_files/docs/default-source/reports/june-2016-report-to-the-congress-medicare-and-the-health-care-delivery-system.pdf [https://perma.cc/R4FQ-JU9U] (2016). The ASP methodology is known as the "buy-and-bill" system. In 2003, Congress made another system available to CMS: the "Competitive Acquisition for Part B Drugs & Biologicals" (CAP). Medicare Modernization Act of 2003, Pub. L. No. 108-173, § 303, 117 Stat. 2066, 2233–55 (codified at 42 U.S.C. 1395u(o)); 42 C.F.R. § 414.908 (2024). While CMS began using this system, it discontinued doing so in late 2008. *Competitive Acquisition for Part B Drugs & Biologicals*, CTRS. FOR MEDICARE & MEDICAID SERVS., https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Part-B-Drugs/CompetitiveAcquisforBios [https://perma.cc/CM3V-QNNX] (Sept. 10, 2024).

44. For requirements and exceptions under Part B, see discussion *infra* Section I.B.

45. *See* CTRS. FOR MEDICARE & MEDICAID SERVS., MEDICARE BENEFIT POLICY MANUAL: CHAPTER 15—COVERED MEDICAL AND OTHER HEALTH SERVICES § 50.4.1 (2024) [hereinafter CMS BENEFIT MANUAL CH. 15], https://www.cms.gov/regulations-and-guidance/guidance/manuals/downloads/bp102c15.pdf [https://perma.cc/FMW5-JFT7]. Since hospitals are paid through a prospective payment system, drugs administered during a hospital stay under Part A are typically not reimbursed separately. For new drugs, CMS make a "pass through" payment to the hospital first two to three years. After that period expires, CMS packages the payment into the new reimbursement rate. 42 U.S.C. § 1395*l*(t)(2)(E); U.S. GOV'T ACCOUNTABILITY OFF., GAO-21-252, MEDICARE PART B: PAYMENTS AND USE FOR SELECTED NEW, HIGH-COST DRUGS (2021). Hospitals must include relevant HCPCS codes on all drugs subject to pass through payment. CTRS. FOR MEDICARE & MEDICAID SERVS., MEDICARE CLAIMS PROCESSING MANUAL: CHAPTER 17—DRUGS AND BIOLOGICALS § 10 (2024) [hereinafter CMS CLAIMS PROCESSING MANUAL CH. 17], https://www.cms.gov/regulations-and-guidance/guidance/manuals/downloads/clm104c17.pdf [https://perma.cc/4YAX-87WV].

46. Until 2003, Medicare did not pay for outpatient prescription drugs. *See* Medicare Prescription Drug, Improvement, and Modernization Act of 2003.

47. 42 U.S.C. § 1395w-104(b)(3)(C); 42 C.F.R. § 423.120(b)(2)(i) (2024). It may also cover drugs provided to an inpatient who has exhausted their lifetime benefit under Part A. CTRS. FOR MEDICARE & MEDICAID SERVS., MEDICARE PRESCRIPTION DRUG BENEFIT MANUAL: CHAPTER 6—PART D DRUGS AND FORMULARY REQUIREMENTS § 20.2.1 (2016), https://www.cms.gov/medicare/prescription-drug-coverage/prescriptiondrugcovcontra/downloads/part-d-benefits-manual-chapter-6.pdf [https://perma.cc/K7KJ-TCJY].

48. CTRS. FOR MEDICARE & MEDICAID SERVS., *supra* note 47, § 30.

classes" of drugs.[49] Functionally, then, CMS will typically cover and pay for FDA-approved retail drugs in protected classes.[50]

CMS's coverage and reimbursement decisions are highly influential. Effects of coverage decisions can be seen in lower prices for private insurers.[51] Although from a slightly different sector, a recent example drives this point home. In 2020, CMS's decision to reimburse LumineticsCore—the first autonomous AI device used in a healthcare setting—drove private payors, which had previously balked at coverage, to cover and pay for the device.[52] While this example involves a device and not a drug, it nevertheless illustrates the influence of CMS on private insurers.

B. Payors as Secondary Gatekeepers for Off-Label Uses

While CMS pays for many FDA-approved drugs, it does not pay for all drugs[53] or all uses of those drugs.[54] The distinction between drugs and drug use is important because CMS may determine whether to pay for a drug based on the specific use to which it is put, rather than the use of the drug generally.[55] And how it makes this determination may depend on the

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49. 42 U.S.C. § 1395w-104(b)(3)(G)(iv)(I)–(VI) (defining protected classes as immunosuppressants, antidepressants, antipsychotics, anticonvulsants, antiretrovirals, and antineoplastics).

50. Plans seem to cover most new drugs within protected classes but often impose requirements like prior authorization to limit access. Many plans do not cover drugs in unprotected classes, which can be lawfully excluded from coverage subject to appeal. Huseyin Naci et al., *Coverage of New Drugs in Medicare Part D*, 100 MILBANK Q. 562, 571–72 (2022).

51. *See* Darius Lakdawalla & Wesley Yin, *Insurers' Negotiating Leverage and the External Effects of Medicare Part D*, 97 REV. ECON. & STAT. 314, 314 (2015). Of course, the precise effect depends on coverage mandates. Mark Duggan & Fiona Scott Morton, *The Effect of Medicare Part D on Pharmaceutical Prices and Utilization*, 100 AM. ECON. REV. 590, 593 (2010).

52. Press Release, Digit. Diagnostics, Historic Proposed CMS Rule Will Allow First-Ever Reimbursement of Autonomous AI in a Healthcare Setting (Aug. 4, 2020), https://www.digitaldiagnostics.com/wp-content/uploads/2020/08/DXS-PressRelease-CMS-Brief.pdf [https://perma.cc/LBJ5-FVH9]; Sophie C. Lee et al., *Trends in Remote Retinal Imaging Utilization and Payments in the United States*, 129 OPHTHALMOLOGY 354, 355 (2022) (demonstrating the extent to which private insurers paid for claims involving remote retinal imaging).

53. This distinction between "drugs" and "drug use" is made for convenience. The FDA approves drugs for particular uses, but because payors cannot always distinguish a drug compound from the use to which it is put, they may restrict use of the drug compound across the board. *See generally* Kelly E. Anderson et al., *Medicare Advantage Coverage Restrictions for the Costliest Physician-Administered Drugs*, 28 AM. J. MANAGED CARE 7 (2022).

54. This discussion is limited to Medicare; Medicaid operates under separate rules.

55. As described below, the plans that administer Part D may also use cost-control measures like step-therapy and prior authorization in lieu of requiring that drugs be prescribed for labeled uses. CTRS. FOR MEDICARE & MEDICAID SERVS., *supra* note 47, § 30.2.2.

conditions under which the drug is used. For drugs administered at a doctor's office under Part B, for example, the legal structure and process of reimbursement are different from drugs purchased at a retail pharmacy under Part D.[56]

What's important to understand about reimbursement writ large, however, is that CMS is the payor but not the administrator. This means that while CMS may determine whether a specific off-label use is "medically accepted" and therefore covered, it often does not. Instead, for most off-label uses, CMS establishes the framework for how private parties that administer Medicare—contractors or insurance plans—should make that determination.[57]

To illustrate, first consider drugs administered in a doctor's office. Here CMS may either use a formal process to determine whether it will cover a drug for all beneficiaries nationwide (a "National Coverage Determination") or let contractors who administer Medicare ("Medicare Administrative Contractors") in different geographic regions make determinations that apply only to the areas they administer ("Local Coverage Determinations"). In the former case, CMS makes a specific finding about how it will cover and pay for an off-label use. For example, CMS originally evaluated and reimbursed verteporfin—a "photosensitive drug" used in photodynamic therapy—for specific uses,[58] but later used a National Coverage Determination to expand reimbursement to other (off-label) uses based on new evidence.[59]

Most decisions, however, are made by local contractors that administer Medicare.[60] Contractors decide whether to reimburse specific off-label uses

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56. Likewise, the person to whom the drug is prescribed may channel decision-making through a different insurance program and reimbursement algorithm. Low-income patients, for example, are covered under Medicaid, not Medicare, though CMS is the ultimate payor for both programs. *See id.*

57. CTRS. FOR MEDICARE & MEDICAID SERVS., *supra* note 28.

58. Sean R. Tunis et al., *Ocular Photodynamic Therapy with Verteporfin for Macular Degeneration*, CTRS. FOR MEDICARE & MEDICAID SERVS. (Nov. 8, 2000), https://www.cms.gov/medicare-coverage-database/view/ncacal-decision-memo.aspx?proposed=N&ncaid=58& [https://perma.cc/8P6J-RJSR].

59. CTRS. FOR MEDICARE & MEDICAID SERVS., NATIONAL COVERAGE DETERMINATION MANUAL: CHAPTER 1 § 80.3 (2024), https://www.cms.gov/regulations-and-guidance/guidance/manuals/downloads/ncd103c1_part1.pdf [https://perma.cc/X48G-ABU4]. The FDA-approved labeling lists as indication for use as classic choroidal neovascularization associated with age-related macular degeneration. *Id.* In 2004, CMS expanded coverage to include subfoveal occult with no classic choroidal neovascularization associated with age-related macular degeneration. *Id.*

60. Medicare Administrative Contractors ("MACs"), which cover twelve geographic regions, make these decisions. *Who Are the MACs*, CTRS. FOR MEDICARE & MEDICAID SERVS., https://www.cms.gov/Medicare/Medicare-Contracting/Medicare-Administrative-Contractors/Who-are-the-MACs#MapsandLists [https://perma.cc/2EWX-Q8TV] (Sept. 10, 2024).

subject to Medicare rules. Medicare sets reimbursement rules through its Benefit Manual,[61] which explains to contractors the evidence CMS considers sufficient to merit payment. This process relies heavily on evidence generated by "compendia": privately run organizations that collect, evaluate, and publish information about off-label uses.[62] By law, different but overlapping compendia govern reimbursement for different categories of drugs.[63]

For cancer drugs, CMS's policy is quite permissive, allowing Medicare Administrative Contractors to reimburse drugs with at least one favorable evaluation in compendia recognized by CMS.[64] To assess support for an off-label use, diagnostic information is required to compare the prescribed use to the evidence supporting it. And diagnostic codes are required when administering oral cancer drugs in these settings.[65] Medicare Administrative Contractors may also impose diagnosis code requirements on particular drugs to limit off-label use.[66] This means that Medicare Administrative Contractors can determine whether a drug is prescribed for a medically accepted indication by consulting the diagnosis and comparing it to the uses evaluated by compendia.

For non-cancer drugs administered in a physician's office, CMS will cover the drug if the contractor "determines the use to be *medically accepted*, taking into consideration the major drug compendia, authoritative medical literature and/or accepted standards of medical practice."[67] Here the list of compendia is smaller than the one for anticancer drugs, but the standard is broad enough to allow reimbursement of a wide range of off-label uses. And since hospitals have their own committees that develop a formulary and evaluate off-label uses, they may be in a position to evaluate such questions more closely than

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61. *See generally Medicare Benefit Policy Manual*, CTRS. FOR MEDICARE & MEDICAID SERVS., https://www.cms.gov/regulations-and-guidance/guidance/manuals/internet-only-manuals-ioms-items/cms012673 [https://perma.cc/2GZX-VEN8]. A related document is the Medicare Claims Processing Manual, which instructs MACs on who to process claims, including the appropriate use of coding for claims and the requirements for each code. *See generally Medicare Claims Processing Manual*, CTRS. FOR MEDICARE & MEDICAID SERVS., https://www.cms.gov/regulations-and-guidance/guidance/manuals/internet-only-manuals-ioms-items/cms018912 [https://perma.cc/VEX7-VGCD].

62. David A. Simon, *Off-Label Speech*, 72 EMORY L.J. 549, 580 (2023).

63. *Compare* 42 U.S.C. §§ 1396r-8(k)(6), (g)(1)(B)(i)(I)–(III), *with* 42 U.S.C. § 1395w-102(e)(1).

64. CTRS. FOR MEDICARE & MEDICAID SERVS., *supra* note 28.

65. CMS CLAIMS PROCESSING MANUAL CH. 17, *supra* note 45, § 80.1.3.

66. *Billing and Coding: Off-Label Use of Rituximab and Rituximab Biosimilars*, CTRS. FOR MEDICARE & MEDICAID SERVS. (Aug. 8, 2024), https://www.cms.gov/medicare-coverage-database/view/article.aspx?articleid=58582 [https://perma.cc/SWY3-AXDG].

67. CMS BENEFIT MANUAL CH. 15, *supra* note 45, § 50.4.3 (emphasis added); 42 U.S.C. § 1396r-8(k)(6) (defining the term "medically accepted indication").

the contractor.[68] While public information concerning how and when contractors reimburse non-cancer off-label uses is not readily available, many inpatient physician services must report a diagnosis code.[69] This makes it at least theoretically possible for a contractor to evaluate (perhaps imperfectly) whether a particular off-label use is medically accepted and hence reasonable and necessary.[70]

Retail drugs have a different framework. Private insurance companies, which administer Medicare's prescription drug benefit, typically make coverage and reimbursement decisions.[71] To participate in Medicare, these private plans must apply and demonstrate that the plan complies with Medicare rules.[72] Rules include requirements on deductibles, annual out-of-pocket limits, cost-sharing, co-insurance, and formulary tiering.[73] Private plans must also follow rules regarding reimbursement of certain drugs, which includes covering uses of drugs that FDA approves and that appear on their formularies.[74]

Unlike drugs used in physician offices, however, CMS does not make coverage determinations as to *any* specific off-label uses. Instead, it specifies *coverage criteria* that plans must follow, including consulting the two "recognized" compendia (AHFS-DI and DrugDex) for retail drugs, and "referenc[ing] all CMS recognized compendia to determine whether there are any supportive citations."[75]

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68. Christy Ciccarello et al., *ASHP Guidelines on the Pharmacy and Therapeutics Committee and the Formulary System*, 78 AM. J. HEALTH SYST. PHARM. 907, 908 (2021).

69. CTRS. FOR MEDICARE & MEDICAID SERVS., MEDICARE CLAIMS PROCESSING MANUAL: CHAPTER 23—FEE SCHEDULE ADMINISTRATION AND CODING REQIUREMENTS § 10.2 (2024), https://www.cms.gov/regulations-and-guidance/guidance/manuals/downloads/clm104c23.pdf [https://perma.cc/632U-GVLV].

70. Whether the contractor or plan sponsor actually does this, however, depends on a different set of incentives. *See, e.g.*, OFF. INSPECTOR GEN. & DEP'T HEALTH & HUM. SERVS., *supra* note 31.

71. *See Part D / Prescription Drug Benefits*, CTR. FOR MEDICARE ADVOC., https://medicareadvocacy.org/medicare-info/medicare-part-d [https://perma.cc/UH84-UJJR]. These are known as Prescription Drug Plans, or PDPs. *Id.*

72. 42 C.F.R. § 423.120 (2024) (describing access, formulary, and drug pricing information requirements); 42 C.F.R. §§ 423.452–.466 (2024) (explaining how Part D rules apply to Part C plans).

73. 42 C.F.R. § 423.104 (2024).

74. *See* 42 U.S.C. § 1395w-102(e) (defining a "covered part D drug" to mean a drug sold on prescription [by reference to Social Security Act ("SSA"), § 1927(k)(2), 42 U.S.C. § 1396r-8(k)(2)] and "any use of a covered part D drug for a medically accepted indication"); 42 C.F.R. § 423.100 (2024); CTRS. FOR MEDICARE & MEDICAID SERVS., *supra* note 47.

75. CTRS. FOR MEDICARE & MEDICAID SERVS., *supra* note 47, § 10.6. Although the reimbursement process for off-label uses under Part B and Part D may seem similar, there are

In both situations—drugs administered at a physician's office or dispensed at a pharmacy—CMS has instituted a decision framework for how to reimburse off-label uses.[76] While this reimbursement framework is not identical to the framework used by private insurance companies, it is quite similar. Some insurance policies even copy language directly from either law or CMS policy on coverage of off-label uses. BlueCross BlueShield of Massachusetts is one example;[77] others are vague.[78] Certain United Healthcare and Cigna plans also mirror CMS policy in significant ways.[79]

And although off-label uses are not often subject to the same high-profile coverage decisions as approved uses, the agency's influence on private insurers is still outsized. For instance, private insurers often rely on the same evaluations of evidence as CMS when reimbursing off-label uses.[80] For cancer drugs the influence has been particularly pronounced, with thirty-six states adopting some form of CMS's reimbursement framework.[81] And even in states and cases where the legislature has not acted, insurers reimbursing off-label uses of prescription drugs tend to rely on the same sources—drug compendia—as CMS.[82]

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important differences. Under Part B, the MAC can consider information and studies outside compendia; PDPs cannot. *Compare id.*, *with* CMS BENEFIT MANUAL CH. 15, *supra* note 45, § 50.4.2. In practice, this makes off-label reimbursement more restrictive for Part D than for Part B. It also provides more discretion for MACs compared to PDPs but allows PDPs to use crude sorting mechanisms to control costs.

76. *See generally* CTRS. FOR MEDICARE & MEDICAID SERVS., *supra* note 47.

77. *Pharmacy Medical Policy: Drug Management & Prior Authorization*, BLUE CROSS BLUE SHIELD MASS., https://www.bluecrossma.org/medical-policies/sites/g/files/csphws2091/files/acquiadam-assets/251%20Drug%20Management%20and%20Prior%20Authorization%20prn.pdf [https://perma.cc/L6ZD-S3KF].

78. *Washington Utilization Management and Exception Process*, AETNA https://www.aetna.com/content/dam/aetna/pdfs/health-care-professionals/washington-utilization-management.pdf [https://perma.cc/L6ZD-S3KF].

79. *Off-Label/Unproven Specialty Drug Treatment*, UNITED HEALTHCARE (July 1, 2024), https://www.uhcprovider.com/content/dam/provider/docs/public/policies/comm-medical-drug/off-label-unproven-specialty-drug-treatment.pdf [https://perma.cc/AZ5C-PX8H]; CIGNA HEALTHCARE, DRUG COVERAGE POLICY: ONCOLOGY MEDICATIONS (2024), https://static.cigna.com/assets/chcp/pdf/coveragePolicies/pharmacy/ph_1403_coveragepositioncriteria_oncology.pdf [https://perma.cc/VS44-YDHF].

80. *See* Joshua Cohen et al., *Off-Label Use Reimbursement*, 64 FOOD & DRUG L.J. 391, 396 (2009). Surprisingly, little has been written about the effects of off-label reimbursement, though the knowledge is common in industry. We do not have good direct evidence on these effects, perhaps in part because most people eligible for Medicare are not enrolled in employer-sponsored or other health insurance coverage (except Medigap).

81. *See* Smieliauskas et al., *supra* note 27, at 56.

82. Cohen et al., *supra* note 80, at 396 (focusing on private prescription drug plans under Medicare). For background on reimbursement of off-label oncology drugs, see U.S. GOV'T

And because CMS relies so heavily on private parties to make off-label coverage and reimbursement decisions, it also displays a striking inversion of what one might expect to result from a government payor. The Medicare rules designed to limit contractor discretion, at least as to certain off-label uses, also enlarge the power of other private organizations that insurers rely on to evaluate information for them: compendia.[83]

C. Two Gatekeepers, Shared Functions

A new picture now emerges. On paper, FDA approves a drug for use under particular conditions. In practice, however, once approved, physicians prescribe the drug off-label under conditions FDA has not necessarily evaluated for safety or efficacy. Yet a consumer's ability to access an off-label use may depend on whether and how CMS reimburses it. In exercising its independent statutory authority to decide whether to reimburse drugs off-label, CMS makes a determination about the relative safety and efficacy of those uses.

Although CMS has some authority to set policy, the authority to make determinations about the relative value of an off-label use falls to private parties—insurers and, more importantly, compendia. This is particularly true in oncology where voluntary organizations have been instrumental in passing legislation in over thirty-nine states embedding compendia and their evaluations in reimbursement policy.[84]

Just how CMS regulates drug use depends on where patients access medications. For off-label uses of drugs administered in a doctor's office (under Part B), CMS may use National Coverage Determinations to set conditions on how the drug will be reimbursed and, hence, used.[85] But often local contractors that administer Medicare, not CMS, make coverage determinations. For coverage decisions concerning off-label uses, CMS instructs local contractors to abide by CMS's manuals and consult existing

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ACCOUNTABILITY OFF., PEMD-91-14, OFF-LABEL DRUGS: REIMBURSEMENT POLICIES CONSTRAIN PHYSICIANS IN THEIR CHOICE OF CANCER THERAPIES (1991).

83. Private payors are also guilty of similar behavior, often outsourcing formulary decisions to pharmacy benefit managers (PBMs), though some of this puzzle may be solved by identifying common ownership between plans and PBMs. *See* Robert B. Goldberg, *Managing the Pharmacy Benefit: The Formulary System*, 26 J. MANAGED CARE SPECIALIZED PHARM. 341, 347 (2020).

84. P. Jane Totten & Thomas F. Goss, *The Impact of Payer Coverage and Reimbursement Policies on Off-Label Use of Anticancer Therapies*, 21 ONCOLOGY ISSUES 36, 36 (2006).

85. *Medicare Coverage Determination Process*, CTRS. FOR MEDICARE & MEDICAID SERVS. https://www.cms.gov/medicare/coverage/determination-process [https://perma.cc/VU4W-AXKY] (Sept. 10, 2024).

published evidence, including requiring them to cover certain anticancer drugs that appear in compendia.[86] In short, Medicare sets rules by which private entities decide whether to reimburse a particular off-label use. Both decisions—by Medicare in setting the policy and by private entities in carrying it out—are guided by the evidence supporting the use.

Many Medicare beneficiaries, though, do not (exclusively) obtain medication in a physician's office or outpatient facility. Instead, they purchase drugs at a retail pharmacy.[87] For these drugs, CMS imposes requirements on the private plans that administer benefits.[88] These rules regulate drug use by limiting access in certain circumstances.[89] In particular, for off-label uses, CMS requires plans to consult compendia to determine whether a use is "medically accepted" and hence reimbursable.[90] Like with other off-label uses, Medicare's rules and insurance plans decisions to cover and reimburse are based on the evidence supporting the prescribed off-label use.[91]

All of this suggests CMS plays an important role in regulating whether and when patients access off-label uses. CMS, along with the private parties that administer it, use evidence to make decisions about whether to cover and pay for an off-label use. In this respect, CMS actions have a similar function to FDA's determination about whether to approve the drug that is normally covered by CMS: it determines relative access to the use of a drug based on a review of safety and efficacy data. Here CMS acts as the Other FDA, using reimbursement to "approve" off-label uses by paying from them.

D. Differences Between Gatekeepers

While CMS's function is similar to FDA's, it is not identical. Part of the difference in methods lies in the function of each agency, as traditionally conceived. FDA evaluates whether drugs should reach the market; CMS

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86. *Compendia 1861 (t)(2)—Anti-Cancer*, CTRS. FOR MEDICARE & MEDICAID SERVS., https://www.cms.gov/medicare/coverage/determination-process/basics/compendia-1861-t2-anti-cancer [https://perma.cc/CX22-PKFW] (Sept. 10, 2024).

87. *See* Lucas A. Berenbrok et al., *Evaluation of Frequency of Encounters with Primary Care Physicians vs Visits to Community Pharmacies Among Medicare Beneficiaries*, 3 JAMA NETWORK OPEN, July 15, 2020, at 1, 1.

88. CTRS. FOR MEDICARE & MEDICAID SERVS., *supra* note 28.

89. *Id.*

90. *Id.*

91. *Id.*

evaluates whether and how to pay for them.[92] This difference is reflected in the statutory mission of each agency, with FDA approving drugs when they are safe and effective for particular uses and CMS reimbursing drugs when they are reasonable and necessary for particular uses.[93]

As a result, each agency may review different types of evidence in distinct ways that reflect their statutory mission and authority. First, consider the type of evidence FDA and CMS review. FDA obtains information directly from drug manufacturers that submit a new drug application.[94] FDA can block market access if a manufacturer fails to produce certain information.[95] Power to withhold approval is significant, and FDA uses it to demand certain kinds of data.

CMS, by contrast, considers publicly available, rather than privately available, data.[96] The reason: CMS lacks the power to block market entry for most drugs, which means it cannot demand data from manufacturers for most drugs like FDA can.[97] Nor can it command FDA share data when making coverage decisions.[98] Indeed FDA may, by its own regulations, be prohibited from sharing it.[99] In some cases, CMS can make coverage determinations that require the drug sponsor to develop evidence, as it did recently with the

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92. Katie Adams et al., *Strengthening Regulatory Collaboration Between FDA and CMS*, BIPARTISAN POL'Y CTR. (Jan. 29, 2024), https://bipartisanpolicy.org/report/strengthening-fda-cms-regulatory-collab [https://perma.cc/X6NC-VND9].

93. *Id.* Courts have agreed. *See, e.g.*, Yale-New Haven Hosp. v. Leavitt, 470 F.3d 71, 84 (2d Cir. 2006).

94. *Development & Approval Process | Drugs*, U.S. FOOD & DRUG ADMIN. (Aug. 8, 2022), https://www.fda.gov/drugs/development-approval-process-drugs [https://perma.cc/RB6Y-6MDJ].

95. *Actions and Enforcement*, U.S. FOOD & DRUG ADMIN. (Oct. 9, 2024), https://www.fda.gov/industry/import-program/actions-enforcement [https://perma.cc/2VPB-8RLN].

96. *See* CTRS. FOR MEDICARE & MEDICAID SERVS., *supra* note 85.

97. Congress recently provided to CMS new authority to obtain information when negotiating certain drug prices IRA. *Inflation Reduction Act and Medicare*, CTRS. FOR MEDICARE & MEDICAID SERVS., https://www.cms.gov/inflation-reduction-act-and-medicare [https://perma.cc/L34D-CHNV] (Jan. 20, 2025). And, as noted above, CMS does have some tools to withhold or restrict payment, such as coverage with evidence development.

98. For general rules on FDA information disclosure, see 21 C.F.R. § 20.1 (2024).

99. 21 C.F.R. § 20.85 (2024) (limiting disclosure to other federal agencies by the terms of 21 U.S.C. §§ 331(j), 360j(c), 360*ll*(d), 360nn(e), 387f(c)).

Alzheimer's drug Aduhelm.[100] But this authority is limited to drugs administered in a doctor's office.[101]

FDA and CMS also evaluate data differently. FDA does much of its regulatory review work "in-house," though it does use committees to make recommendations.[102] But CMS, as explained in Section I.B. above, typically does neither. How CMS considers evidence depends on both (1) the program under which drug reimbursement is requested and (2) the type of drug for which reimbursement is requested.[103]

In some cases, however, CMS's process resembles FDA's. When CMS makes a National Coverage Determination, for example, it typically enlists experts from a broad range of fields to provide advice on coverage.[104] Here the analysis is done both by CMS and its coverage advisory committee, similar to how FDA consults advisory committees in its approval decisions.[105] But not all coverage decisions are made by CMS using National Coverage Determinations. In fact, many decisions are made by local contractors or drug plans that administer Medicare.[106] In either case, private entities make coverage determinations,[107] often by relying on third parties (e.g., compendia) to both supply them with and evaluate information.[108]

CMS and FDA are different in another way, as well: CMS has more tools to directly regulate drug use than FDA has to limit entry. FDA's ability to withhold access is extremely powerful, though it is binary: drugs are approved (for particular uses) or not. While FDA has some tools to modulate

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100. Press Release, Ctrs. for Medicare & Medicaid Servs., CMS Finalizes Medicare Coverage Policy for Monoclonal Antibodies Directed Against Amyloid for the Treatment of Alzheimer's Disease (Apr. 7, 2022), https://www.cms.gov/newsroom/press-releases/cms-finalizes-medicare-coverage-policy-monoclonal-antibodies-directed-against-amyloid-treatment [https://perma.cc/HPT7-YY7V].

101. *Id.*

102. 21 C.F.R. § 14.1 (2024); INST. OF MED., FOOD AND DRUG ADMINISTRATION ADVISORY COMMITTEES 5 (Richard A. Rettig et al. eds. 1992).

103. *See supra* Section I.B.

104. *See, e.g.*, Notice of Revised Process for Making Medicare National Coverage Determinations, 68 Fed. Reg. 55634, 55640 (Sept. 26, 2003); *Medicare National Coverage Process*, CTRS. FOR MEDICARE & MEDICAID SERVS., https://www.cms.gov/Medicare/Coverage/DeterminationProcess/Downloads/8a.pdf [https://perma.cc/2423-FMUB].

105. The information considered and the manner in which it is considered is not identical. *Compare* CTRS. FOR MEDICARE & MEDICAID SERVS., FACTORS CMS CONSIDERS IN REFERRING TOPICS TO THE MEDICARE EVIDENCE DEVELOPMENT & COVERAGE ADVISORY COMMITTEE (2006), https://www.cms.gov/medicare-coverage-database/view/medicare-coverage-document.aspx?mcdid=10 [https://perma.cc/U5L3-SD8B], *with Advisory Committees*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/advisory-committees [https://perma.cc/ETJ8-EG86].

106. *See infra* Section II.B.

107. *See supra* Sections I.B, I.D.

108. *See infra* Section II.B.2

market access—like Risk Evaluation and Mitigation Strategies ("REMS") and mandatory confirmatory trials—many argue that FDA has not used them with much rigor.[109] CMS decisions to reimburse are also binary, but the decision framework has built-in flexibility in modulating access, which can be channeled through various mechanisms that make a binary decision more or less likely—what we might call *access probability*.[110] Contractors that administer Medicare can use plans to modulate or influence drug use through prior authorization, step therapy, and coverage determinations.[111] Because contractors operate independently from CMS payments but within its rules, CMS does not universally control access probability, which varies considerably from plan to plan and state to state.

Perhaps just as importantly, ability and willingness to pay can influence access probability. Individuals with enough money, strong enough preferences, and a licensed prescribing physician can purchase drugs for off-label uses without insurance. One recent example is some patients' ability and willingness to pay cash for off-label uses of the weight loss drug Ozempic, which FDA approved as an adjunctive treatment for type-2 diabetes.[112] While off-label access to most Americans was limited, those willing and able to pay $1,000 per month could access it through firms that connected them to physicians who would prescribe it off-label.[113] For drugs

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109. *See* Holly Fernandez Lynch et al., *Extending the US Food and Drug Administration's Postmarket Authorities*, JAMA HEALTH F., No. e231313, at 2–3 (June 9, 2023), https://jamanetwork.com/journals/jama-health-forum/fullarticle/2805891 [https://perma.cc/9ACS-FYBA]; s*ee also* Bishal Gyawali et al., *Regulatory and Clinical Consequences of Negative Confirmatory Trials of Accelerated Approval Cancer Drugs: Retrospective Observational Study*, BMJ, n1959, at 6 (Sept. 9, 2021), https://www.bmj.com/content/bmj/374/bmj.n1959.full.pdf [https://perma.cc/B4S8-R8QK]; Holly Fernandez Lynch & Alison Bateman-House, *Facilitating Both Evidence and Access: Improving FDA's Accelerated Approval and Expanded Access Pathways*, 48 J.L. MED. & ETHICS 365 (2020); Matthew Herder, *Pharmaceutical Drugs of Uncertain Value, Lifecycle Regulation at the US Food and Drug Administration, and Institutional Incumbency*, 97 MILBANK Q. 820 (2019); Sarah S. P. DiMagno et al., *Accelerated Approval of Cancer Drugs—Righting the Ship of the US Food and Drug Administration*, 179 JAMA INTERNAL MED. 922, 923 (2019).

110. The term means the probability that one will be able to access a drug. Two critical factors that affect access probability are ability and willingness to pay.

111. *See, e.g.*, *Prior Authorization, Step Therapy, and Quantity Limits*, WELLCARE, https://wellcare.azcompletehealth.com/drug-pharmacy/prior-authorization.html [https://perma.cc/486M-N7N7].

112. *Ozempic (Semaglutide) Injection for Subcutaneous Use*, NOVO NORDISK (Dec. 2017), https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/209637lbl.pdf [https://perma.cc/N635-948R].

113. Katie Palmer, *Where Are Patients Getting Their Prescriptions for GLP-1 Drugs like Wegovy and Ozempic?*, STAT (Aug. 10, 2023), https://www.statnews.com/2023/08/10/wegovy-

like Ozempic, CMS may influence access probability, but it will not determine access.

Despite these differences, however, the two agencies share a functional similarity: they act as gatekeepers of innovation. FDA's gatekeeping function is important to driving innovation because firms must produce data demonstrating safety and efficacy before the drug reaches the market.[114] Often, that gatekeeping function is the primary one with which regulators and scholars are concerned because the other gatekeeper, CMS, will pay for the drug as a matter of course. But in certain cases like off-label uses, CMS's decision to cover and reimburse is functionally similar to FDA's decision to approve a drug. In deciding whether to reimburse an off-label use, CMS approves the use through payment—a decision that can influence the type and quantity of new drugs. Firms, indeed, have shown a particular interest in off-label use as a strategy to increase sales.[115] CMS has the ability to influence access probability, and hence sales, through its decision to reimburse off-label uses.

At the same time, however, the analogy to FDA is not perfect. CMS differs from the FDA in what evidence of off-label use it considers, how it considers it, and its ability to regulate use.[116] Despite these differences, the similarity in the gatekeeping function between the two agencies enables a reconceptualization of drug regulation—namely, in some cases there are two gatekeepers rather than one that affect innovation: FDA, which regulates market access, and CMS, which acts as the Other FDA by regulating off-label drug use. This reconceptualization provides a useful framework for thinking through the proposals by pro-market scholars to change FDA approval. To do that, however, one needs to understand existing proposals to reform FDA approval of prescription drugs, something considered in the next Part.

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ozempic-weight-loss-telehealth-prescriptions [https://perma.cc/J4CR-MUPV]. For a simple example, a Google search for "accessing Ozempic" displayed an advertised link to "15 Min Dr. Consult for Rx—Ozempic Online" offered by PlushCare, though the website itself is more balanced. *Ozempic (Semaglutide) Prescription Online*, PLUSHCARE, https://plushcare.com/ozempic-online [https://perma.cc/XL4Y-G9ST].

114. *See* U.S. FOOD & DRUG ADMIN., *supra* note 95.

115. *See* Benjamin Berger et al., *Regulatory Approval and Expanded Market Size* 13 (Nat'l Bureau of Econ. Rsch., Working Paper No. 28889, 2021), https://www.nber.org/papers/w28889 [https://perma.cc/4HD5-8QK2].

116. *See supra* Section I.A.

II. REFORMING THE GATEKEEPERS

This Part uses the conceptualization of CMS as the Other FDA to identify and evaluate pro-market scholars' proposals to alter FDA approval. Section II.A situates the discussion within the context of pro-market scholars' criticisms of and proposed reforms to FDA. It suggests that one proposal (FDA approval based only on safety) could be adapted to fit within the description of Part I of this Article (by using CMS to regulate efficacy). Section II.B then addresses an important conceptual objection to the reform suggested in Part B (as well as some of the reforms suggested by economists in Part A)—that separating safety and efficacy is impossible. Section II.C expounds on this conceptual problem and identifies several others: reimbursement, evidence evaluation, and post-marketing surveillance. The purpose of this Section is to show that although this new potential system has challenges, they are not necessarily insurmountable.

A. Proposals to Reform the Initial Gatekeeper

Pro-market scholars have suggested different modifications to FDA approval authority. In general, these scholars propose to generate a more efficient state of affairs by privatizing or outsourcing some or all of FDA's regulatory activities.[117] For example, some propose making FDA "primarily a certifier of certifiers, rather than a certifier of products"[118] while others urge an "informed choice" model that allows most drugs to market without approval but mandates drug manufacturers provide information about drug effects to consumers.[119] Still, others seek to increase efficiency by either

117. This was also part of a bill introduced in 1997, which was ultimately discarded in favor of the 1997 FDAMA. *See* Drugs and Biological Products Reform Act of 1996, H.R. 319, 104th Cong. § 2; *see also* David A. Hyman & William E. Kovacic, *Risky Business: Should the FDA Pay Attention to Drug Prices Health & Medicine*, 40 REGULATION 22, 24 (2017) (proposing FDA consider drug costs in its approval decision).

118. Henry I. Miller, *A Proposal for FDA Reform*, 1 NAT'L REV. DRUG DISCOVERY 642, 647 (2002).

119. Dale H. Gieringer, *The Safety and Efficacy of New Drug Approval*, 5 CATO J. 177, 181 (1985); *see* Lewis A. Grossman, *AIDS Activists, FDA Regulation, and the Amendment of America's Drug Constitution*, 42 AM. J.L. & MED. 687, 633–34 (2016) (citing Gina Kolata, *Odd Alliance Would Speed New Drugs*, N.Y. TIMES, Nov. 26, 1988, at 9).

reducing the need for physician prescriptions[120] or enabling FDA to rely on certain foreign drug regulatory agencies' approval of that same use.[121]

While at least one pro-market scholar believes there is no market failure for FDA to solve and, therefore, no need for the agency,[122] this position is an outlier. Among the pro-market scholars, a more common and well-defended position—first argued for empirically by Sam Peltzman,[123] but also espoused by commentators like Richard Epstein,[124] Milton Friedman,[125] Alex Tabarrok,[126] and members of the CATO Institute[127]—is that FDA standards should revert to those of the pre-1962 drug law, where FDA has the statutory authority to block market entry only for reasons related to "safety."[128]

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120. Sam Peltzman, *Prescription for Lower Drug Prices: More OTC Transitions for the Record*, 41 REGULATION 2, 2 (2018). Whether this would increase out-of-pocket costs is uncertain.

121. Kenneth I. Kaitin, *FDA Reform: Setting the Stage for Efforts to Reform the Agency*, 31 DRUG INFO. J. 27, 32 (1997). This, of course, creates new incentives for drug companies to seek approval where it is easiest, and may have a variety of unintended consequences. Commentators have discussed some obstacles to this. *See* Kassel, *supra* note 17, at 115–25. Another variation is to use approval in another country as a presumption against which FDA must argue. *See* Theodore Ruger, *FDA Reform and the European Medicines Evaluation Agency*, 108 HARV. L. REV. 2009, 2016–20 (1995).

122. Klein, *supra* note 12, at 316–18.

123. PELTZMAN, *supra* note 11, at 75–79; Peltzman, *supra* note 8, at 38; *see* Henry G. Grabowski et al., *Estimating the Effects of Regulation on Innovation: An International Comparative Analysis of the Pharmaceutical Industry*, 21 J.L. & ECON. 133, 141 (1978); Thomas, *supra* note 9, at 497. *But see* Gieringer, *supra* note 119, at 182–83 (arguing that an informed-choice policy is "superior to any new-drug approval system"). Peltzman's research efforts were in some part directed and supported by his advisor, George Stigler, who "arranged for his former student Sam Peltzman to produce a paper on the 'costs' of the Kefauver–Harris Amendments, pledged funds from his Walgreen Foundation to finance Peltzman's research, and oversaw its progress." Edward Nik-Khah, *Neoliberal Pharmaceutical Science and the Chicago School of Economics*, 44 SOC. STUD. SCI. 489, 492 (2014) (footnotes omitted).

124. EPSTEIN, *supra* note 7, at 10.

125. *See* John Phelan, *Milton Friedman on the FDA*, AM. EXPERIMENT (July 17, 2020), https://www.americanexperiment.org/milton-friedman-on-the-fda [https://perma.cc/BU8W-RMDK].

126. *See* Alexander T. Tabarrok, *Assessing the FDA via the Anomaly of Off-Label Drug Prescribing*, 5 INDEP. REV. 25, 25 (2000) (suggesting that the practice of allowing clinicians to prescribe drug off-label without efficacy review by FDA is logically inconsistent with prohibiting physicians from prescribing new drugs until they have undergone an efficacy review).

127. Doug Bandow, *The FDA Can Be Dangerous to Your Health*, CATO INST. (Nov. 11, 1996), https://www.cato.org/commentary/fda-can-be-dangerous-health [https://perma.cc/6MPS-VVMJ].

128. Under the 1938 statute, the process was not, as the term is used today, a premarket approval: drug applications would "become effective" automatically after sixty days unless FDA either extended the period for review or denied the application. Federal Food, Drug, and Cosmetic Act, Pub. L. No. 75-675, § 505(b)–(d), 52 Stat. 1040, 1052 (1938).

A safety-only role seems unpalatable to many, however, because they fear ineffective drugs will flood the market.[129] Perhaps this worry is exacerbated, rather than mollified, because the market already contains a number of ineffective off-label uses—and even likely ineffective on-label ones (such as Aduhelm).[130] Section I.C showed, however, that CMS constrains potentially ineffective off-label uses (and some on-label uses) by deciding whether to reimburse the drug—and that in doing so, it performs an FDA-like function. Furthermore, the safety-only system is particularly attractive—at least relative to the other pro-market proposals—because of its presence before 1962, making the concept not just theoretically, but practically, plausible.

This raises the question: if CMS already acts like FDA with respect to off-label uses by evaluating efficacy information, why not simply let it do so for on-label uses as well? Why not, in other words, satisfy pro-market scholars' desire for speed and access with other scholars' desire for safety and effectiveness by implementing a system where FDA regulates only drug safety by gatekeeping approval and CMS regulates efficacy by gatekeeping reimbursement?[131] Because CMS's FDA-like role has been overlooked, so too has this possibility. Economists like Peltzman come the closest, but even they do not consider (i) whether the system is coherent and, if so, (ii) what effects it would have on the larger regulatory and legal environment.[132] Section II.B considers (i). Section II.C develops a new proposal that incorporates both Peltzman's suggestion and the new understanding of CMS as a gatekeeper of certain drug use. Part III uses the new framework to assess (ii).

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129. This is a slightly different concern than a fear of false positives. Most analyses of false positives assume an analysis of the drug on the relevant attribute. Here that would mean an evaluation of efficacy. But since efficacy is not evaluated as such, a concern that ineffective drugs will flood the market is more accurately described as a fear that the market will not sufficiently regulate drugmakers.

130. I do not mean to imply that those who worry about ineffective drugs are unconcerned with ineffective off-label drugs. Many are, and they could also reply that *adding* to the number and scope of ineffective uses is even more worrisome than simply having physicians prescribe ineffective off-label uses. *See, e.g.*, Fernandez Lynch et al., *supra* note 109, at 3–6.

131. As noted at the outset of this Article, CMS is one of many payors, and this proposal would not necessarily be limited only to a single governmental payor.

132. There is vast literature responding to Peltzman, including recent work arguing that Peltzman didn't account for, among other things, the substitution effects of unsafe or ineffective alternatives in the absence of treatment. *See* Casey B. Mulligan, *Peltzman Revisited: Quantifying 21st-Century Opportunity Costs of Food and Drug Administration Regulation*, 65 J.L. & ECON. S355, S377 (2022).

B. Safety Versus Efficacy: A False Dichotomy

Some pro-market scholars are skeptical of the efficacy requirement. Work on the history of FDA, however, shows that the skepticism may be based on an inaccurate picture of pre-1962 drug regulation.[133] Dan Carpenter and others have demonstrated that even prior to 1962—the year that Congress imbued FDA with the authority to prevent drugs from entering the market unless they were efficacious as well as safe—FDA had been busy evaluating efficacy in making its safety determinations.[134] Perhaps the point is rather unsurprising given that it is impossible to conclude that a drug is safe without knowing for what and how it would be used,[135] something the law recognized before 1962.[136]

What all this illustrates is that suggestions, such as Peltzman's, to return drug approval to a pre-1962, safety-only regime are somewhat misinformed about the process of FDA review during that time.[137] Perhaps characterizing FDA as focused "only" on safety in 1940 was appropriate, but the description was inapt by the 1950s and flat wrong by 1960. Not only that, but safety is a

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133. Interestingly, just before Peltzman's work in 1972, another economist (Jondrow) noted that "the short term downward trend [in therapeutic advances] started before the amendments." James Marshall Jondrow, A Measure of the Monetary Benefits and Costs to Consumers of the Regulation of Prescription Drug Effectiveness 164 (1972) (Ph.D. dissertation, University of Wisconsin) (on file with author). Yet, Jondrow did not consider that the decrease in new therapeutics was itself the result of an FDA increasingly attuned to efficacy.

134. DANIEL P. CARPENTER, REPUTATION AND POWER: ORGANIZATIONAL IMAGE AND PHARMACEUTICAL REGULATION AT THE FDA 75, 113, 115, 120 (2010); s*ee also* Gieringer, *supra* note 119, at 183. *See generally* PETER TEMIN, TAKING YOUR MEDICINE: DRUG REGULATION IN THE UNITED STATES (1980) (explaining how FDA's regulatory framework, even before the 1962 amendments, evolved to control drug availablity and assess risks, including considerations beyond mere safety). FDA regulations often explicitly required evidence of efficacy. *See, e.g.*, Regulations Under Sections 201, 505 and 702 of the Federal Food, Drug, and Cosmetic Act, 3 Fed. Reg. 1846, 1847 (July 23, 1938) (explaining what constitutes a new drug and mandating drug sample requirements); Regulations for the Enforcement of the Federal Food, Drug, and Cosmetic Act, 21 Fed. Reg. 5576, 5578 (July 25, 1956) (implementing more expansive regulations, including a form of application that required "full reports of all investigations that have been made to show whether the drug is safe for use" and other requirements); Subchapter D—Drugs for Human Use: Reorganization and Republication, 39 Fed. Reg. 11680, 11721 (Mar. 29, 1974) (updating regulations after 1962 amendments and requiring applicant to provide "substantial evidence consisting of adequate and well-controlled investigations" supporting efficacy).

135. CARPENTER, *supra* note 134, at 120, 130.

136. Under the 1938 Act, FDA determined whether a drug was "safe for use under the conditions prescribed, recommended, or suggested in the labeling thereof." Federal Food, Drug, and Cosmetic Act, Pub. L. No. 75-675, § 201(p), 52 Stat. 1040, 1041–42 (1938) (defining "new drug"). Notably, the type of "safety" evidence required by § 505(b) of the 1938 Act differs markedly from what is required today. *See* CARPENTER, *supra* note 134, at 120, 130.

137. *See* discussion *supra* note 133.

relative term—and not just in theory. Carpenter's work shows that safety as a concept was subject to change, expanding considerably with the development of modern science and the power of FDA.[138] A regime premised on safety, then, must make room not just for efficacy, but also for the changing conceptual scope of safety.

Pro-market scholars, however, have more nuanced views that respond to this criticism. They recognize that safety and efficacy are both relative and subjective.[139] Risk, while unavoidable, is relative because it varies by patient and disease type.[140] Taking a drug may risk death but if the available alternative is certain death, it may be a risk worth taking.[141] For this reason, some argue that drug approval should not depend merely on the risk of a false positive or negative as such, but rather on the risk of a false positive or negative *given the burden of the disease*.[142] Lowering FDA approval standards in this way is consistent with both the relative nature of risk and its subjectivity: individuals, rather than the government, are best positioned to make determinations about the appropriate safety-efficacy tradeoffs that match their own interests and risk tolerance.[143]

Understood this way, "separating" safety and efficacy is not incoherent. Pro-market scholars' proposals reflect a tolerance for a reduced evidentiary burden to obtain FDA approval, rather than a strict divorce of safety from efficacy. Safety without efficacy is conceptually possible, then, but only by flushing from its definition certain conceptions of efficacy. Even with this definitional maneuver, however, FDA must evaluate safety under different conditions of use. Just how FDA evaluates the question of safety will depend on the approach it takes to approving drugs, which is explored further in the next Section.

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138. The process was gradual but still quite real, with FDA routinizing and standardizing not just drug applications and safety demonstrations but its demands of NDAs. CARPENTER, *supra* note 134, at 140, 150–51. Courts may have played a role, but that was as much a part of the regulatory scheme as anything else. Rsch. Lab'ys v. United States, 167 F.2d 410, 412 (9th Cir. 1948)*; see also* Richard A. Merrill, *The Architecture of Government Regulation of Medical Products*, 82 VA. L. REV. 1753, 1764 (1996).

139. Gieringer, *supra* note 119, at 180.

140. *See* Ruger, *supra* note 121, at 210.

141. *See* Daniel Klein, *Policy Medicine Versus Policy Quackery: Economists Against the FDA*, 13 KNOWLEDGE TECH. & POL'Y 92, 93–94 (2000).

142. *See* Leah Isakov et al., *Is the FDA Too Conservative or Too Aggressive?: A Bayesian Decision Analysis of Clinical Trial Design*, 211 J. ECONOMETRICS 117, 134 (2019).

143. *See* Gieringer, *supra* note 119, at 180; Alex Tabarrok, *Is the FDA Too Conservative or Too Aggressive?*, MARGINAL REVOLUTION (Aug. 26, 2015), https://marginalrevolution.com/marginalrevolution/2015/08/is-the-fda-too-conservative-or-too-aggressive.html [https://perma.cc/MM6H-4HQ2].

C. Questions for the New Dual Gatekeeping System

While it is theoretically possible to reduce the initial evidentiary burden, it is not possible to separate safety from efficacy entirely—or to judge the safety of a drug without understanding the context in which it is used. All this raises the question of what it means for a drug to be "safe," along with three other issues that the new system would need to address: reimbursement, evidence evaluation, and post-marketing surveillance. The goal of each subsection is not to specify the standard that FDA could use. It is, instead, to identify the potential ways of addressing the questions that arise in an approval system based only on safety. In other words, this Section shows only that it is possible to meet these objections but does not specify the most desirable way of doing so. In making this argument, it trades the rather unhelpful safety-versus-efficacy dichotomy for a more helpful one: market entry versus reimbursement.

1. Safety: Market Entry

What does it mean for a drug to be safe? This subsection explores how the FDA might implement an approval process that evaluates the safety of one or more uses by identifying requirements for market entry, rather than safety as such. For the moment, however, assume FDA approves a drug as "safe" for a particular use, consistent with drug approval standards between 1938 and 1962. The next question is, what criteria will FDA use to determine whether a drug is safe for a particular use?

Since safety is tied to efficacy, FDA must find some way to fold the latter into a framework built around the former.[144] This makes the critical issue how much and what kind of efficacy information should be required before approval.

Here we can imagine various scenarios, all of which assume at least some kind of *initial* clinical trial as to *some particular use* (though not necessarily the use applied for). This may take the form of Phase I and II trials on the applied-for use or Phase I, II, or III trials on the same or a similar drug for related indications. The manufacturer may provide data about, and FDA might assess, the *likelihood* of efficacy for the applied for use(s), using some method of extrapolation from existing data, the mechanism of action, and/or the clinical and research history of similar medications.

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144. Under a disclosure model, FDA would merely state the risks associated with the drug and consumers could decide whether to take it.

Initial data from a Phase I trial, for example, may suggest that a drug is efficacious for one condition, and the mechanism for action might also suggest its potential efficacy for other uses as well. FDA could use publicly and privately available information on the likelihood that the drug would be efficacious and use that probability to set safety thresholds. If the drug is a selective serotonin reuptake inhibitor ("SSRI"), for example, FDA might look to previous SSRIs, their clinical and research history, and their safety profile. Technology, such as artificial intelligence and machine learning, may aid in prediction and assessment.[145] FDA could also have varying forms of power to demand information related to uses. For example, FDA's authority could operate on a sliding scale: less power to demand data on more credible candidate uses, and more power to demand data on uses that have little or no safety information. Of course, the more power one provides to FDA to demand information, the more like the current system the new one is likely to look.

Another option is for FDA to *assume* the drug is at least minimally effective when making safety determinations. This would allow FDA to opine on a level of acceptable risk without commenting on whether the drug is effective. For example, an elevated risk of cardiovascular disease (such as heart attack or stroke) associated with use of a drug designed to treat pancreatic cancer may be an acceptable level of risk assuming the drug is minimally effective; but the same level of risk may not be acceptable for use as an anti-inflammatory.[146]

To discourage manufacturers from attempting to skirt the safety requirement by simply submitting a drug for use at a minimal dose, federal law could impose an evidentiary requirement, coupled with a good faith requirement, that the manufacturer have a reasonable belief that the drug is a potential candidate to treat a particular condition and has some potential to be efficacious (see discussion above).[147] One could imagine, for example, a

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145. In this vein, FDA recently announced guidance expanding the types of evidence that could support drug approval. *See* U.S. DEP'T OF HEALTH & HUM. SERVS. ET AL., DEMONSTRATING SUBSTANTIAL EVIDENCE OF EFFECTIVENESS WITH ONE ADEQUATE AND WELL-CONTROLLED CLINICAL INVESTIGATION AND CONFIRMATORY EVIDENCE: GUIDANCE FOR INDUSTRY (2023). FDA has also been active in trying to evaluate a framework for using "real world evidence" in supplemental NDAs for new indications. 21st Century Cures Act, Pub. L. No. 114-255, § 3022, 130 Stat. 1033, 1096–98 (2016) (codified at 21 U.S.C. § 355f); *Real-World Evidence*, U.S. FOOD & DRUG ADMIN. (Sept. 19, 2024), https://www.fda.gov/science-research/science-and-research-special-topics/real-world-evidence [https://perma.cc/6XVR-LEME].

146. To some extent, this raises a new question: what does it mean to be minimally effective? Answering definition questions like these with precision is outside the scope of this Article.

147. Terms like "reasonable belief" and "potential candidate" would, of course, need some definition.

requirement that preliminary study data suggest the drug have some potential for efficacy in treating a particular condition. Again, the precise contours of the regulation are not important here; what is important is that the law requires the manufacturer to develop and disclose robust safety data on likely uses of the drug.

Both of these approaches assume that the new system would follow FDA's historical approach, which has required manufacturers to submit safety data on a drug for use under particular intended conditions—though the demands on manufacturers would not match what is required under current regulations. This would preserve the formal existing distinction of on- and off-label uses. But using safety, and not efficacy, as the touchstone of approval will diminish the meaningfulness of the on/off-label distinction despite its formal existence. Currently the on/off-label distinction roughly marks the difference between a use with strong evidence of efficacy and one without it (or at least one without FDA-vetted evidence). In the new system, however, the distinction would signal the difference between some evidence of safety but say much less about the uses potential efficacy.

How much the distinction says depends on the rigor of the approval standard. If the safety evaluation is weak enough, a drug that is approved without any efficacy requirement means it may not work for *anything*. This upends part of the off-label bargain, which gives physicians both the flexibility to try new things and, critically, the knowledge that the drug at least (probably) works for something.[148] Increasing access to a drug for off-label uses without a countervailing informational benefit (e.g., efficacy information) could justify requiring safety information for each *potential* use of the drug.

While this would raise costs, the new system could enhance the safety requirement more efficiently by mandating that the drug manufacturer seek approval or submit safety data on certain "identified uses." For example, when Neurontin went to market, the manufacturer may have had evidence that the drug could be used for a number of different conditions—and it promoted it for a variety of them.[149] One could imagine a safety standard that

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148. This statement must be qualified. FDA approval does not actually provide a guarantee that a drug works, either for a particular person or a group of people. While this is true for any drug, the concern is more acute for drugs that are approved under the accelerated approval pathway because of reduced evidentiary standards.

149. The firm also had no evidence the drug could be used for other conditions but promoted it for those uses anyway. *See* Tracy Staton, *Pfizer Adds Another $325M to Neurontin Settlement Tally. Total? $945M*, FIERCE PHARMA (June 2, 2014), https://www.fiercepharma.com/sales-and-marketing/pfizer-adds-another-325m-to-neurontin-settlement-tally-total-945m [https://perma.cc/

required the manufacturer to identify likely uses of the drug and provide safety information for those uses.

Just how "identified uses" are defined could vary, as could the mechanisms for evaluating them. For example, one approach could require manufacturers to identify "likely uses" of a drug based on existing data and projections about physician usage and marketing. FDA could then apply the same safety standards to all potential identified uses—evaluating the relative risk posed to individuals taking a drug for a particular use—and the manufacturer would have to satisfy the safety standards for each identified use to be approved.

While this approach may reduce the overall burden on FDA, it could have unintended effects. Depending on liability, for example, manufacturers would be incentivized to be over- or underinclusive in their decision to identify uses. If manufacturers face a significant liability risk for identified uses, they may err on the side of including only those with the safest uses—even if they meet various mandated evidentiary thresholds. Conversely, if the law provides a liability shield to manufacturers, they may identify a broader range of uses with questionable safety profiles to increase sales.

To limit gaming of the system, one could impose some legal requirements that the identified uses reflect a reasonable and diligent effort at identification of likely uses, imposing civil and criminal penalties on violators. Another approach would allow the FDA to independently identify uses and evaluate them according to the same or similar standards. FDA could make projections about the most likely uses based on its expertise, the data submitted by the manufacturer, and physician prescribing models. Part of this process could also require manufacturers to identify uses it reasonably and in good faith believes physicians are most likely to prescribe. This approach would increase the quality of information about safety but would increase costs associated with approval. Some mixture of these approaches is also possible.

Underlying the tradeoff between liability and number of identified uses is another between costs and information. Approval based on showing only one safe use would reduce costs but provide minimal information, while one that is based on other potential and reasonably likely uses would increase costs but also increase the quantity (and potentially the quality) of information about the drug. More requirements on manufacturers, FDA, or both to identify uses will increase the amount of information produced and the cost to approve a drug. Conversely, fewer requirements will reduce the cost of approval and the amount of information about potential uses of the drug.

2TJ4-45S8]. This resulted in settlements with the federal government totaling hundreds of millions of dollars. *Id.*

Whatever approach the new system employs, the approval standard must balance the need for adequate safety information that applies to the most predictable uses with the additional costs of obtaining safety information for each additional use. While this relationship may reduce to a simple function with declining marginal costs for each additional identified use, it may also be considerably different. In some cases, the safety profile of a drug at one dose, population, or method of administration may be unpredictably different than in another dose, population, or method of administration. In other cases, the differences may be minimal and predictable.

Whatever the safety standard, it is conceptually possible to formulate one that does not depend entirely on the existing efficacy standard. In other words, criteria for safety do not need to consider evidence of efficacy in the same way that FDA does now or did before or after 1962. At the same time, however, safety and efficacy are inextricably linked, and problems associated with this linkage can be mitigated but not eliminated. The purpose of this subsection was merely to show that any of these variations, in economic terms, shift in FDA's utility calculus, lowering the threshold risk-benefit analysis required for approval. This changes both the cost of approval and the quantity of information produced from it. A key feature of this risk-benefit analysis, however, is that it will be less robust than the risk-benefit analysis that CMS would perform when deciding reimbursement questions—questions to which this Article now turns.

2. Efficacy: Reimbursement

If FDA approves a use, CMS must decide whether and when to reimburse it. But because CMS is not obligated to pay for drugs under this new system, novel reimbursement approaches open up.[150] Here there are three aspects of reimbursement: use-based coverage, reimbursement amount, and reimbursement metrics.[151]

First, CMS would have the power to explicitly and more completely cover drugs based on *use*. "Coverage" indicates whether CMS will pay some amount for at least one use of a drug. CMS may cover one use but not another, or it may not cover *any* use. Its decision can be driven by evidence specific to that use, much in the same way it currently reimburses certain off-label

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150. Of course, these approaches do not depend on the system I describe. They could be evaluated (and utilized) independently of any assessment or implementation of my proposal.

151. Another aspect of reimbursement not discussed here is coverage, which refers to whether an insurer will pay any amount for a particular use. While this subsection assumes not all drugs will be covered, it discusses those drugs as not being reimbursed for any amount.

uses. But its power would be broader, effectively regulating every approved (and potentially unapproved) use by deciding whether to cover them.

Second, CMS has discretion to reimburse covered uses in different *amounts* based on the quality of evidence supporting the use. A drug may be approved to treat depression based on strong but not overwhelming evidence and approved to treat migraines on weaker evidence. CMS may decide that the evidence for both uses merits coverage but different reimbursement amounts. For example, CMS may cover eighty percent of the cost of the drug when used to treat depression and twenty percent when used to treat migraines. Here reimbursement serves as both a carrot and a stick, proportionately deterring use except in cases where it is most likely to be effective.

Third, CMS can tie reimbursement to different *metrics*. Historically CMS could not, for example, consider a drug's cost or its comparative effectiveness when deciding whether to cover and pay for it.[152] While cost may have indirectly factored into deciding whether drugs were "reasonable and necessary," historically it has not been a driving component that determined coverage or reimbursement. This changed significantly in 2022, when Congress gave CMS the authority to negotiate certain drug prices and mandated consideration of factors that bear on cost and comparative effectiveness.[153] A system like the one described in this Article, however, would make it easier to build on these recent changes to include more explicit consideration of comparative effectiveness, social value, or some other criteria in making coverage and reimbursement decisions, not just those that involve drug pricing for selected drugs. Just as importantly, the metrics could be applied to each *use* of the drug, rather than to the drug itself, reducing reliance on crude proxies designed to limit use (like step therapy, prior authorization, and formularies) without eliminating them entirely.[154]

Finally, CMS could have more power to tie reimbursement to *evidence development*. CMS currently can use the National Coverage Determination

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152. *See* Jacqueline Fox, *Medicare Should, but Cannot, Consider Cost: Legal Impediments to Sound Policy*, 53 BUFF. L. REV 577, 610 (2006).

153. Inflation Reduction Act of 2022, Pub. L. No. 117-169, §1194(e)(2), 136 Stat. 1818, 1846–47 (codified at 42 U.S.C. § 1320f-3); Memorandum from Meena Seshamani, Deputy Adm'r & Dir. of the Ctr. for Medicare, Ctrs. for Medicare & Medicaid Servs., to Interested Parties (June 30, 2023), https://www.cms.gov/files/document/revised-medicare-drug-price-negotiation-program-guidance-june-2023.pdf [https://perma.cc/KV59-GPPE].

154. In theory, some ability to price by use is possible by making less drastic changes, such as requiring diagnosis codes on all prescriptions. *See infra* Section III.A.1.

process to set conditions of coverage, including evidence development.[155] While CMS has recently used this tool to limit reimbursement for the high-profile Alzheimer's drug Aduhelm, that action is not the norm.[156] The authority to limit coverage—or payment amounts—until there is sufficient evidence of efficacy to merit higher reimbursement rates could take different forms. For example, the Institute for Clinical and Economic Review ("ICER"), an independent body that evaluates comparative effectiveness, suggested pricing the drug at the marginal cost of production until confirmatory trials have taken place.[157] The Medicaid and CHIP Payment and Access Commission ("MACPAC") has proposed increasing the "minimum rebates" and, after a certain number of years, increasing the inflationary rebate for accelerated approval drugs Medicaid reimburses until the manufacturer completes confirmatory trials and receives traditional FDA approval.[158] And, of course, the process could incorporate aspects of CMS's newfound power to negotiate certain drug prices based on, among other things, comparative effectiveness data.

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155. *See Guidance for the Public, Industry, and CMS Staff: Coverage with Evidence Development*, CTRS. FOR MEDICARE & MEDICAID SERVICES (Nov. 20, 2014), https://www.cms.gov/medicare-coverage-database/view/medicare-coverage-document.aspx?MCDId=27 [https://perma.cc/6SNX-FRWM].

156. *See* J.D. Chambers & P.J. Neumann, *Discrepancies Between FDA Approval and CMS Coverage for Drugs and Devices*, VALUE HEALTH, May 2013, at A3; *see also* C. Joseph Ross Daval & Aaron S. Kesselheim, *Authority of Medicare to Limit Coverage of FDA-Approved Products: Legal and Policy Considerations*, 183 JAMA INTERNAL MED. 999, 999 (2023). Scholars have also argued that FDA can help mitigate this problem by requiring confirmatory studies in special cases where evidence is less than is typically demanded. *See* Lynch et al., *supra* note 109, at 1–2.

157. ANNA KALTENBOECK ET AL., INST. FOR CLINICAL & ECON. REV., STRENGTHENING THE ACCELERATED APPROVAL PATHWAY 31 (2021), https://icer.org/wp-content/uploads/2021/04/Strengthening-the-Accelerated-Approval-Pathway-_-ICER-White-Paper-_-April-2021.pdf [https://perma.cc/6KXF-5Y7T].

158. MEDICAID & CHIP PAYMENT & ACCESS COMM'N, REPORT TO CONGRESS ON MEDICAID & CHIP 2, 9, 13–15 (2021), https://www.macpac.gov/wp-content/uploads/2021/06/June-2021-Report-to-Congress-on-Medicaid-and-CHIP.pdf [https://perma.cc/CG57-985T]; *see* JENNIFER PODULKA, HEALTH MGMT. ASSOCS., MEDICARE COVERAGE OF DRUGS THAT RECEIVE FDA ACCELERATED APPROVAL 8 (2022), https://www.healthmanagement.com/wp-content/uploads/Medicare-Drug-Coverage-IB-FINAL.pdf [https://perma.cc/L27E-2BD2] (suggesting a twenty-five percent increase in rebates for Part B drugs); *see also* Letter from Michael E. Chernew, Medicare Payment Advisory Comm'n Chair, to Chiquita Brooks-LaSure, Adm'r, Ctrs. for Medicare & Medicaid Servs. (Feb. 10, 2022), https://www.medpac.gov/wp-content/uploads/2022/02/Feb22_NCD_Monoclonal_Alzheimers_MedPAC_comment_v2_SEC.pdf [https://perma.cc/6558-FLPB] (arguing that CMS should not automatically reimburse drugs approved by FDA).

3. Evidence Evaluation

If CMS is tasked with evaluating effectiveness, how will it do so? One option is to retain the existing system. Recall that currently CMS performs an evidentiary analysis in-house only for National Coverage Determinations.[159] For most decisions, however, Medicare Administrative Contractors and PDPs do most of the evaluation. And, in the context of off-label uses, a significant amount of evaluative work is done by third-party compendia, which CMS ostensibly regulates and contractors use to decide whether an off-label use can be reimbursed under CMS rules.

On the one hand, a compendia-based approach has significant efficiencies that the public sector lacks. And at least some of the glaring deficiencies—conflicts of interest, transparency on data collection and use, and reliability—can probably be addressed with minimal regulatory oversight.[160] On the other hand, pushing the efficacy evaluation to CMS moves what has been a traditional center of expertise (FDA) to another agency (CMS) that does not have the same expertise. Although CMS may acquire more of this expertise through the new drug negotiation process, FDA still enjoys an advantage over CMS based on existing institutional resources, competence, and memory. What's more, reimbursement decisions that use efficacy may replicate the pathologies of FDA, just in a different agency.

All this raises the question of how much power and capacity CMS should or could have to demand information, evaluate information, and determine reimbursement rates. While not within the scope of this Article, any serious proposal to implement this new system would have to analyze these questions. Consider, for example, FDA's current authority to withhold marketing authorization until the manufacturer provides additional requested information—information that might otherwise never be seen. In a system where a drug's use is approved but not necessarily paid for, CMS might have similar power, but it would depend on how the legislation granting such power is structured. Strong and weak versions are possible. For thought experiment purposes, this Article considers a situation in which CMS has significant authority to refuse to cover and reimburse drugs when evidentiary thresholds are not met, and to set rates of reimbursement based on existing supporting evidence.

Based on this description, three observations are worth making. First, realigning the system in this way will entail high up-front costs, likely with a

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159. *See supra* Section I.D. Even here the process is not necessarily performed by CMS staff, but rather a significant amount of the work is done by outside experts who serve on advisory committees to CMS.

160. *See* Simon, *supra* note 62, at 595–601.

long tail, and some increased fixed costs to maintain the new evaluation system. Second, this increase in costs may be partially offset by both a decrease in FDA's costs for approval and CMS's newfound authority. Third, if CMS obtains new authority, it must match that authority with expertise by coordinating with FDA, outsourcing the work to private parties or advisory committees, or increasing its own technical capacities.

As noted below, if a proposal to decrease FDA authority shifts costs rather than reduces them, then this may decrease the attractiveness of the proposal on welfare grounds. Shifting costs (via the functions of agencies), however, may result in a more efficient system, particularly if other benefits of the shift outweigh its costs.

4. Post-Marketing Surveillance

Increasing the supply of drugs based on weaker evidence of efficacy raises additional concerns about what happens once a drug is on the market. What obligations should manufacturers have to collect information? What powers should FDA have to mandate information collection, post-confirmatory trials, or post-market restrictions (e.g., REMS)? Currently, manufacturers have post-market obligations to "submit to FDA adverse drug experience information" associated with the use of their drugs,[161] and to investigate, and provide information requested by FDA concerning, "adverse drug experience[s] that [are] both serious and unexpected."[162] Manufacturers also have to submit detailed annual reports about new information they have obtained regarding the drug's safety and effectiveness.[163] And they are required under state tort law to update and request approval of label changes "to reflect newly acquired information."[164]

But they cannot report side effects about which they lack knowledge—and their data comes from case reports, studies, and physicians, who are often required by ethics codes to report them.[165] Manufacturers also have an obligation under tort law to both keep abreast of the literature and update the

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161. 21 C.F.R. § 314.80(c)(1)–(2) (2024) (describing the timing and content requirements of various reporting obligations). In some cases, FDA has the power to require post-market studies, though it has rarely exercised this power with much effect. *See* Lynch et al., *supra* note 109, at 1–2; 21 C.F.R. § 314.510 (2024).

162. 21 C.F.R. § 314.80(c)(1)(ii) (2024). Special rules apply to drugs in the initial stages of development. *See, e.g.*, 21 C.F.R. § 312.32 (2024).

163. 21 C.F.R. § 314.81 (2024).

164. 21 C.F.R. § 314.70(c)(6)(iii) (2024); *see infra* Section III.A.5.b.

165. AM. MED. ASS'N, CODE OF MED. ETHICS Op. 8.8 (2022), https://code-medical-ethics.ama-assn.org/sites/default/files/2022-08/8.8.pdf [https://perma.cc/D5QY-6BP4].

drug label with certain new risks for labeled indications.[166] But millions of prescriptions are written every day, and it is difficult to track even a fraction of those that result in an unwanted side effect.

To track safety-related issues, FDA maintains a large electronic system, the Sentinel System, which contains data from collaborating academic medical centers, healthcare systems, and health insurance companies ("Data Partners"), including Aetna, Humana, and several others.[167] Participation in the program is optional, and FDA has only as much access as the Data Partner allows.[168]

Sentinel's voluntary participation is emblematic of FDA's limited authority to mandate data collection and disclosure by manufacturers and physicians. Although manufacturers have some continuing duties to report adverse events under federal and state law, the duties can sometimes heavily rely on private law claims to do enforcement work. And much of FDA's authority to limit manufacturer behavior is predicated on the agency obtaining new information about the safety of a drug. For example, FDA may limit the ways in which drugs are prescribed when it "becomes aware of new safety information" and determines a limitation "is necessary to ensure that the benefits of the drug outweigh the risks of the drug."[169] For drugs that are potentially harmful or exhibit inherent toxicity, FDA can use REMS to require manufacturers to mandate training or certification for prescribers or dispensers, limiting the use of the drug by specifying the conditions on dispensing.[170] FDA may also order manufacturers to perform confirmatory trials for certain drugs, though it has mostly done so rather meekly.[171]

FDA's role as a gatekeeper, then, is supplemented by its role as a scout. In a safety-only regime, these roles might switch. If FDA approves more drugs on less evidence, many of the safety-related issues that necessarily arise only after a drug has been on the market will multiply, suggesting a greater

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166. *See infra* Section III.3.b. As discussed below, this generally applies only to on-label risks, but there are some off-label risks to which it applies as well. Tort law may also impose some limits on what firms can say in light of information they collect.

167. *Who Is Involved*, SENTINEL INITIATIVE, https://www.sentinelinitiative.org/about/who-involved [https://perma.cc/NN73-E3ZZ]; *see* Food and Drug Administration Amendments Act of 2007, Pub. L. No. 110-85, § 905, 121 Stat. 823, 944–49 (codified at 21 U.S.C. § 355).

168. *See How Sentinel Gets Its Data*, SENTINEL INITIATIVE, https://www.sentinelinitiative.org/about/how-sentinel-gets-its-data [https://perma.cc/2JMC-WED3].

169. 21 U.S.C. § 355-1(a)(2)(A).

170. *Id.* § 355-1(f).

171. Lynch et al., *supra* note 109, at 1–2.

role for FDA in monitoring safety-related events.[172] Congress might respond and provide to FDA additional monitoring authority or enable it to impose on manufacturers (and others) additional information collection and reporting requirements.

Additional functions, however, would increase costs, potentially offsetting the benefits of a safety-only system. But the alternative—relying on existing FDA surveillance and the tort system, including large class actions and medical monitoring—may not be attractive. Litigation often generates data piecemeal and at great cost. And FDA authority may not be robust enough given that safety risks often cannot be known fully until a drug has been widely used for a substantial period of time—something potentially exacerbated if safety evaluations involve trials with fewer participants or different types of data than a full approval would normally generate.[173] While this Article does not comment on either the desirability of new FDA powers or the precise form they would take under this new system, it emphasizes that reducing FDA's gatekeeping function may lead to an increase in its monitoring power—or it might require it. In short, drug development costs may fall but costs to monitor the use of drugs may increase.

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Already we can see how changing the approval standard complicates the cost-benefit analysis. Moving to a "safety" standard raises important and difficult questions about what it means for a particular use to be safe without being effective; how CMS would evaluate and reimburse drugs; and whether additional post-market monitoring should be required. But this is just the beginning. Implementing this approach and coupling it with efficacy-based reimbursement would change other aspects of drug approval—in some cases imposing significant costs. But it also has important benefits that the current system may lack.[174] The next Part considers these costs and benefits.

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172. This much was suggested by FDA Commissioner Andrew Von Eschenbach, who advocated for faster FDA reviews based on a variety of factors. *See* Andrew Von Eschenbach & Ralph Hall, *FDA Approvals Are a Matter of Life and Death*, 110 MO. MED. 110, 110–111 (2013).

173. Barbara J. Evans, *The Future of Prospective Medicine Under the Food and Drug Administration Amendments Act of 2007*, *in* FDA IN THE TWENTY-FIRST CENTURY: THE CHALLENGES OF REGULATING DRUGS AND NEW TECHNOLOGIES 568 (Holly Fernandez Lynch & I. Glenn Cohen eds., 2015).

174. In some sense, a safety-only system would rely on the private market to price drugs. This proposal differs from a market-oriented approach in that reimbursement by the federal government would often set market price, or at least relevant market metrics, for pricing by private insurers.

III. COSTS AND BENEFITS

This Part explores the costs and benefits of the proposed regulatory regime, flagging and analyzing issues that scholars have not yet fully considered on either side of the ledger. Section III.A articulates three categories of costs: compatibility costs, operational costs, and downstream costs. Section III.B identifies the potential benefits, some of which have been neglected, of moving to the proposed system.

A. Costs

This Article divides costs into five different categories. *Compatibility costs* are costs related to altering the existing system to make it technically and administratively compatible with the new system—something akin to what economists call switching costs.[175] *Equality costs* are the costs to patients of accessing drugs. *Development costs* are the costs of developing a drug, including those associated bench research, clinical trials, and regulatory approval. *Operational costs* are the administrative and other costs associated with operating the new system once compatibility is established. And *downstream costs* are those caused by the changes required by the new system, such as alterations to legal regimes like advertising and tort liability. Two features distinguish compatibility from downstream costs. First, the former concern the costs associated with making internal technical and administrative changes to allow a system to function; the latter concern costs associated with the external interaction between the new system (that has been made compatible) and existing bodies of law. Second, compatibility costs are relatively straightforward and mechanical; downstream costs, by contrast, are more uncertain and depend on normative judgments about the scope and role of law in the new system.

Not all of the costs I discuss here are necessarily associated with pro-market scholars' proposals to get FDA out of the efficacy business—and some may be more significant or salient than others. For example, a system that eliminated FDA's efficacy requirement but did nothing else would not incur all of the costs associated with this proposal, though it would incur different ones. And switching costs, to take one example, may not be a significant concern because they are entailed by any system-wide change. At the same time, however, pro-market scholars' proposals are often thin on details, and part of the purpose of this Article is to consider costs these

175. *See* Joseph Farrell & Carl Shapiro, *Dynamic Competition with Switching Costs*, 19 RAND J. ECON. 123, 123 (1988).

scholars have not yet discussed. In this light, some costs may be perfectly reasonable to consider, even under versions of FDA drug approval that pro-market scholars have floated.

1. Compatibility Costs

Implementing this new system requires rendering it compatible with the existing one. To reimburse a drug based on efficacy for a particular use, the payor needs to know the disease or condition for which the physician prescribed it. Without this information, a new system is impossible.[176]

CMS does not typically collect this information. That's because although it requires diagnosis codes[177] on certain drugs administered in a doctor's office,[178] CMS doesn't generally require diagnosis codes for other drugs administered in a doctor's office or those obtained at a retail pharmacy (e.g., drugs covered under Part B or Part D drugs).[179] Without a diagnosis code, CMS has no easy means of determining for what condition or disease the physician prescribed the drug.[180]

To obtain information about drug use, CMS could require diagnosis codes on all prescriptions.[181] Without taking this step, the agency might have to

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176. A system without this change is perfectly possible. But it would also be practically difficult to implement. Since firms could not price discriminate based on use without diagnosis information, they would have to charge the same price for all uses, essentially replicating the current pricing system and eliminating much of the benefit of reducing the efficacy requirement.

177. Diagnosis codes are numerical codes that represent a particular diagnosis, usually as defined by international standards, such as the International Classification of Diseases, the most recent version of which is the ICD-11. *See International Classification of Diseases 11th Revision*, WORLD HEALTH ORG. [WHO], https://icd.who.int/en [https://perma.cc/7Z4W-RTG9].

178. *See* CMS CLAIMS PROCESSING MANUAL CH. 17, *supra* note 45, §§ 80.1–.2 (requiring diagnosis codes for some cancer drugs and oral anti-emetics as part of chemotherapy).

179. States implementing Medicaid may also impose requirements for diagnosis codes for certain medications. *See, e.g.*, *Drugs Requiring Transmission of a Diagnosis Code*, MINN. DEP'T OF HUM. SERVS., https://mn.gov/dhs/partners-and-providers/policies-procedures/minnesota-health-care-programs/provider/types/rx/drugs-requiring-diagnostic-code.jsp [https://perma.cc/9Y9B-ZPMQ] (Feb. 9, 2018).

180. Some have proposed requiring diagnosis codes. *See* Christi A. Grimm & Julie K. Taitsman, *Why Drug Prescriptions Should Include Diagnoses*, STAT NEWS (Mar. 1, 2021), https://www.statnews.com/2021/03/01/why-drug-prescriptions-should-include-diagnoses [https://perma.cc/8CCL-QXM6]; *see also* Ankur Ramesh Shah et al., *Adding Diagnosis Codes to Prescriptions: Lessons Learned from a Quality Improvement Project*, 15 J. MANAGED CARE PHARMACY 508, 510 (2009); Benjamin N. Roin, Solving the Problem of New Uses 58–65 (Oct. 14, 2016) (unpublished manuscript), https://www.bu.edu/law/files/2016/10/Solving-the-Problem-of-New-Uses-Ben-n.-Roin.pdf [https://perma.cc/XX87-RWF4].

181. Ryan Abbott & Ian Ayres, *Evidence and Extrapolation: Mechanisms for Regulating Off-Label Uses of Drugs and Devices*, 64 DUKE L.J. 377, 405–07 (2014).

resort to prior authorization requirements for all drugs, something that would be cost-prohibitive and politically unpalatable.[182] The action is not merely hypothetical. CMS already conducted a pilot program to examine the feasibility of requiring diagnosis codes,[183] and as noted above, it currently requires diagnosis codes for certain drugs under Part B.[184] To implement a diagnosis code requirement nationally, the agency could use its statutory authority to expand the requirement to all drugs reimbursed under Medicare.[185]

States can also take action to reduce CMS's role in requiring diagnosis codes. Some states, for example, already require diagnosis codes for particular circumstances or drugs—such as when made as part of a claim under workers' compensation benefits[186] and when a physician prescribes controlled substances.[187] These laws could serve as models, perhaps with relevant stakeholders meeting to draft a uniform law that requires physicians to include diagnostic codes or information on prescriptions.

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182. While prior authorization is normally triggered by specific drugs, CMS has used it for certain patient populations. From 2013 to 2014, CMS instituted a blanket prior authorization requirement for all Part D prescriptions for patients enrolled in hospice. In 2014, however, CMS revised its policy to require prior authorization only for four prescription drug classes (which it considered the most common). Memorandum from Amy K. Larrick, Medicare Drug Benefit & C & D Data Grp. Acting Dir., Ctrs. for Medicare & Medicaid Servs., & Laurence Wilson, Chronic Care Pol'y Grp. Dir., Ctrs. for Medicare & Medicaid Servs., to all Part D Plan Sponsors & Medicare Hospice Providers (July 18, 2014).

183. *See* ARIZ. REV. STAT. ANN. § 32-1964 (2024); *see also* ARIZ. ADMIN. CODE § R4-23-407 (2024) (Board of Pharmacy regulations); *see also* ARIZ. ADMIN. CODE § R4-23-408 (2024) (requiring a "problem list" of each patient but based on patient self-reports). CMS conducted a pilot program in Arizona to determine how to improve this system where it requested participants to use ICD-9 codes on all prescriptions. Shah et al., *supra* note 180, at 508.

184. *See* discussion *supra* Section I.B.

185. CMS could require this under Part B using 42 U.S.C. § 1395l(e), which states that "[n]o payment shall be made to any provider of services or other person under this part unless there has been furnished such information as may be necessary in order to determine the amounts due such provider or other person under this part for the period with respect to which the amounts are being paid or for any prior period." 42 U.S.C. § 1395l(e) (2024). Similar authority exists for CMS to mandate diagnostic information on prescriptions as a condition for participating plans in Part D. *See generally* 42 U.S.C. § 1395w–112(a) (2022) (granting CMS broad authority to mandate certain conditions on manufacturers as a prerequisite to participation in Part D plans).

186. *E.g.*, *The Impact of Prescription Drug Pricing on Workers' Compensation Claims*, LEGAL INTELLIGENCER, https://www.law.com/thelegalintelligencer/2021/10/05/the-impact-of-prescription-drug-pricing-on-workers-compensation-claims [https://perma.cc/4ZA7-P4V8].

187. CAL. HEALTH & SAFETY CODE § 11190 (West 2024); OHIO ADMIN. CODE § 4729-5-15(B)(14)(b)(i) (2024) (requiring diagnosis codes for prescribed controlled substances); NEV. REV. STAT. § 453.162(e)(3) (2023) (same); 216 R.I. CODE R. 20-20-4.4L (2022) (same); *see also* ALASKA DEP'T HEALTH & SOC. SERVS., ICD-10 DIAGNOSIS CODE OPIOID PRESCRIPTION REQUIREMENTS GUIDANCE (2017), https://www.commerce.alaska.gov/web/Portals/5/pub/PHA_MedicaidOpioidGuidance_2018.12.pdf [https://perma.cc/BCL3-49TR].

There are other costs to changing the system. Depending on how CMS evaluates evidence and reimburses drug use, the government might need to create new units or departments within the Department of Health and Human Services to do pricing evaluations, though it may develop this expertise using its new authority to negotiate some drug prices.[188] Some or all of these costs could be mitigated by relying on and bolstering independent organizations, like ICER, that evaluate drug cost-effectiveness.[189] Relying on compendia to occupy a more robust role in drug data collection and evaluation is also possible, but would require additional oversight to ensure good quality information on which CMS could make reimbursement decisions.[190] At the very least, CMS will require additional resources to evaluate how much it should pay for drug uses. Perhaps this will not be as difficult given CMS's new role as negotiator under the Inflation Reduction Act, but it will still require a significant amount of effort to evaluate uses that CMS currently does not evaluate at all in-house.

Finally, there are costs to changing FDA's role. On the one hand, reducing FDA's role may reduce costs *for FDA*. On the other hand, someone must evaluate efficacy, which will shift costs elsewhere, perhaps raising them for CMS. FDA may also have increased responsibilities to monitor drug use in the real world, potentially raising costs of bulking up the Sentinel system and policing post-marketing requirements on manufacturers.

2. Equality Costs

Although this new system increases access, it may do so only for those with the willingness and ability to pay—the wealthy.[191] Not all consumers, however willing, will be able to pay for drugs that are not reimbursed (or are reimbursed at low rates). For example, nearly 80 million low-income adults and children rely on public insurance programs, and many may not be able to afford the out-of-pocket costs when insurance will not pay (enough) for a

188. *See, e.g.*, Inflation Reduction Act of 2022, Pub. L. No. 117-169, § 1194(e)(2), 136 Stat. 1818, 1843 (codified at 42 U.S.C. §1320f-3).

189. *See ICER's Impact*, INST. CLINICAL & ECON. REV., https://icer.org/who-we-are/history-impact [https://perma.cc/U6PG-RVT2]; *see also, e.g.*, NAT'L INST. HEALTH & CARE EXCELLENCE, https://www.nice.org.uk [https://perma.cc/AK24-WW9Q].

190. *See* Simon, *supra* note 62, at 556–58.

191. Welfare may also be defined as something other than satisfaction of preferences as measured by willingness and ability to pay.

particular use.[192] Access to certain *uses*, then, will be limited for those with low incomes—raising concerns over the equal distribution of the system's benefits.[193]

While this presents a concern, it is also exactly the kind of result we would expect—and hope for—in a system that modulates use through efficacy. Indeed, this is precisely the point of the proposal:[194] reimbursement limits access to uses with weak supporting evidence and expands access to uses with strong supporting evidence. In other words, if CMS accurately and reliably identifies the relative efficacy of individual uses, then patients will be priced out of uses that lack strong evidence of efficacy. Those without the ability to pay may be deprived of some treatments, but, if the system works properly, it is precisely those treatments that are not worth paying for (yet). And the flip side of this is perhaps justified on fairness grounds: the risks of new uses of uncertain benefit would be borne by the willing and wealthy.[195]

It is true, however, that income will, in some cases, determine access. To justify this inequality, the overall welfare improvements of this system must outweigh its alternatives. This could be true because although the new system would restrict some access to some uses, it would generate more innovations and broader access to those innovations. A system that ensured greater access would likely dampen drug development since the public fisc cannot absorb these costs in the same way as the private market. This means that fewer drugs and uses would be developed in an equal-access system than in one that had income-based access to uses based on efficacy. If the improvement is efficient, then the general solution is to tax and redistribute, not to choose a less efficient system. That said, countervailing arguments may show that this new system reduces welfare compared to another that ensures equal access. While this Article identifies and remains open to these possibilities, it does not comment on them further.

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192. *October 2024 Medicaid & CHIP Enrollment Data Highlights*, MEDICAID, https://www.medicaid.gov/medicaid/program-information/medicaid-and-chip-enrollment-data/report-highlights/index.html [https://perma.cc/ZC6Q-EYMS].

193. To circumvent insurance and provide access to their patients, some physicians may deliberately miscode for a covered use. Allowing or ignoring this behavior would threaten the core of use-based pricing that underpins the new system. Therefore, the law must provide a strong disincentive for physicians to inaccurately record the diagnosis on the prescription. Although penalizing or punishing physicians for fraudulent prescriptions may seem harsh from an access perspective, it must be part of any system designed to reimburse based on the efficacy of particular uses.

194. *See infra* Section III.B.3.

195. This argument has serious problems since just as a person's income should not determine their access to medication, it also should not determine whether they are modern-day guinea pigs.

3. Development Costs

With lower barriers to entry, the costs of drug development may decrease.[196] At the same time, however, greater access to drugs and uses may increase the costs associated with developing evidence of efficacy for each use since those who can afford access to a drug will likely buy it instead of participating in a two-arm, placebo-controlled trial. In this new system, then, recruiting and running clinical trials may require additional financial inducements or new technologies that raise costs. And some recruitment will fail altogether, potentially eliminating new efficacy information; but it is also possible that such uses are not developed in the current system. In short, these costs are uncertain, likely to vary widely by disease and drug, and should be considered when evaluating the welfare effects of the new system.

4. Operational Costs

Operational costs are overall costs required to operate a new approval and reimbursement system.[197] Under this new system, operational costs would include increased resources directed at CMS to administer the new reimbursement apparatus. The extent of these costs, however, is uncertain. Depending on the model selected, CMS may simply expand its use and regulation of compendia, in which case the increase (at least in public expenditures) would be relatively modest.[198] Or it may do all the work in-house, substantially raising the costs of operating the new system.

At the same time, however, the new system would likely reduce FDA's costs. Since it would not need to evaluate the same kinds or quantity of data, it would not need as many staff. Of course, if FDA's authority to surveil drug use or bring enforcement actions increases, costs will also increase, though the government may be able to offset—at least on the government ledger—these increases through settlements or verdicts achieved through enforcement of federal law. Likewise, increased surveillance may have other benefits, discussed below.

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196. *See infra* Section III.B.1.

197. Here I exclude "enforcement" from operational costs not because the costs fall outside the category, but rather because explaining them entails a discussion of changes that affect downstream costs, which I explain in the next subsection.

198. For an explanation of compendia practices and how such a system might work, see Simon, *supra* note 62, at 580–601.

A significant question not answered here is exactly how work would be split between the agencies, and whether they could or should communicate.[199] Depending on the institutional role of each agency, interagency communication may raise or decrease costs over the long term. For example, better communication and data sharing between the agencies could expedite reimbursement decisions. But if communication procedures became too burdensome, the costs of communication may exceed the benefits of siloing behavior. To reduce administrative clutter, CMS might require new powers to demand the same information in the same form that an applicant provided to FDA for approval. While such processing would be duplicative, the incentive for private firms to obtain reimbursement may be a more effective incentive to push information to CMS than the one that requires FDA to share information with CMS within some specified time period.

5. Downstream Costs

Perhaps the most significant but least discussed set of costs are those that result from a change in the system and that are not associated strictly with technical compatibility or operations. Although the amount of the potential costs is uncertain, what is certain is that there will be downstream costs—costs associated with making choices about how the legal system will accommodate or adapt to the new regime. This Section identifies and discusses the downstream costs related to labeling, advertising, and liability.[200] Discussion of these issues is not meant to catalogue or quantify all potential costs; rather it's meant to identify the potential of a small change to have large ramifications on existing legal regimes and alter the cost-benefit analysis.

a. Label, Labeling, and Advertising

FDA derives its primary power from its legal authority to police drug labels and labeling. Labels are the written material physically attached to the drug's immediate container but not including package inserts.[201] Labeling means something broader and includes almost any written, graphic, or printed

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199. *See generally* Rachel E. Sachs, *Administering Health Innovation*, 39 CARDOZO L. REV. 1991 (2018) (discussing how "inter-agency and intra-agency coordination models" among top administrative agencies affect drug pricing).

200. These are not the only potential downstream changes—they also include legal rules related to reimbursement and post-marketing surveillance described above. But these three legal regimes are the most obviously impacted by a seemingly simple change to FDA approval.

201. 21 U.S.C. § 321(k).

communication about the product by the manufacturer.[202] FDA requires labeling to contain warnings and precautions (risks associated with taking it), contraindications (who should not take it), and boxed warnings (serious risks such as life-threatening ones or how such risks can be avoided).[203]

Because FDA approval enables market entry only with a label and labeling that specifies *use of the drug under particular conditions*,[204] approval decisions limit how manufacturers can market and promote an approved drug. Labeling, in particular, is closely tied to drug advertising and promotion because federal law—and courts interpreting it—have defined most labeling as encompassing advertising.[205] Prescription drug advertising, specifically, is also regulated by FDA.[206]

Labeling's edifice, like so much else in drug regulation, is built around evidence of efficacy. What distinguishes a legal advertisement for a supplement and one for a drug may well be its *validated* claim that the product can treat a particular disease or condition.[207] In a world without efficacy requirements, what kind of claims will manufacturers be allowed to make?[208]

Manufacturers, of course, will still be constrained by federal and state laws, including those prohibiting deceptive and unfair business practices, false advertising, and fraud. Existing requirements that prevent manufacturers from having labeling that is "false or misleading in any particular"[209] may be carried over without change, or they may be modified. Regardless, the evidence required for approval will limit manufacturers' claims about efficacy. At some level, however, drug manufacturers must be able to make stronger claims than manufacturers of other FDA-regulated

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202. 21 C.F.R. § 201.1 (2024); 21 U.S.C. § 321(m) (defining labeling to include written, printed, or graphic matter "accompanying" the drug).

203. U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY: WARNINGS AND PRECAUTIONS, CONTRAINDICATIONS, AND BOXED WARNINGS SECTIONS OF LABELING FOR HUMAN PRESCRIPTION DRUG AND BIOLOGICAL PRODUCTS—CONTENT AND FORMAT 3, 8, 11 (2011). These requirements were part of new labeling regulations promulgated in 2006. Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products, 71 Fed. Reg. 3922, 3924 (Jan. 24, 2006) (codified at 21 C.F.R. pts. 201, 314, 601).

204. *See* 21 U.S.C. § 355(4).

205. *See, e.g.*, 21 U.S.C. § 321(m)–(n); 21 C.F.R. § 202.1; United States v. Rsch. Lab'ys, 126 F.2d 42, 45 (9th Cir. 1942). There is only one recent case citing *United States v. Research Laboratories*, but the proposition still seems to stand. *See* Healey v. I-Flow, LLC, 853 F. Supp. 2d 868, 878 n.3 (D. Minn. 2012)

206. 21 C.F.R. § 202.1.

207. There may, of course, be other reasons that differentiate the two.

208. Another question is how efficacy claims will be prosecuted and evaluated. FDA or DOJ may learn information about drug effects through discovery in litigation over advertising.

209. 21 C.F.R. § 201.56(a)(2) (2024).

products, such as supplements, which do not undergo even a safety review by FDA.[210] Without the ability to make claims stronger than supplements, FDA approval may not provide a strong enough incentive to develop drugs in the first instance. Firms may find it more profitable to sell supplements, or cars, instead.

Changing labeling and advertising rules also could increase costs associated with enforcement. Post-hoc adjudication of efficacy also requires (to varying degrees) post-hoc adjudication of the merits of claims about efficacy. And this kind of adjudication may develop its own jurisprudence that evaluates efficacy by standards that satisfy the First Amendment but not the patient. It is unclear whether these increased costs would be offset by the additional information consumers and physicians may receive about drugs—depending on the direct-to-consumer advertising rules—which could alert them to new treatments.[211] Given the increased risk created by lack of information about the drug and the potential reliance on the physician to evaluate public information about it, the benefits seem doubtful.

A potential way to reduce costs is by using a system that allows advertising based on evidence. Since manufacturers will have to justify reimbursement by demonstrating some level of efficacy, using that evidence to regulate advertising makes regulatory sense. A grading system used by CMS or some independent body, which has been proposed and explored in various contexts, could be used to evaluate evidence.[212] Evidence grades could then be linked to specific types of advertising activity.[213] Of course, developing this system would create additional costs that would need to be weighed against the benefit of the information provided. Relying on existing enforcement mechanisms, such as enforcement through the Federal Trade Commission, would still require adjustment to the new approval framework.

Perhaps government intervention would be unnecessary and the private market would, in the face of little regulation, do more to police the private market. Organizations like the American Medical Association ("AMA") may

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210. *Questions and Answers on Dietary Supplements*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/food/information-consumers-using-dietary-supplements/questions-and-answers-dietary-supplements [https://perma.cc/S987-ZYJP] (Feb. 21, 2024).

211. *Compare* Julie M. Donohue et al., *A Decade of Direct-to-Consumer Advertising of Prescription Drugs*, 357 NEW ENG. J. MED. 673, 674 (2007), *with* Bradley T. Shapiro, *Promoting Wellness or Waste? Evidence from Antidepressant Advertising*, 14 AM. ECON. J. MICROECON. 439, 443 (2022).

212. *See, e.g.*, Daniel B. Klein & Alexander Tabarrok, *Do Off-Label Drug Practices Argue Against FDA Efficacy Requirements? A Critical Analysis of Physicians' Argumentation for Initial Efficacy Requirements*, 67 AM. J. ECON. & SOCIO. 743, 767 (2008).

213. *See* Simon, *supra* note 62, at 558.

become actively involved in vetting information and penalizing those that advertised bogus or questionable claims, much as they did in the early twentieth century.[214] Perhaps publications or associations could modernize the AMA's historic tactic of "institutionaliz[ing] the work of muckrakers . . . [by setting] up an office to pursue fraudulent drugs and shame publishers of journals and newspapers into dropping all advertisements of patent medicines."[215]

Advertising, information dissemination, and scientific research, however, have changed markedly since the early 1900s. Social media, television, websites, and journal publications all provide information to consumers, and organizations like the AMA do not exert as much control over these newer media sources as they do over the media of old. So while voluntary organizations or the private market may regulate away bad information, it is at least equally likely that such information would impose an additional cost on public and private actors. Private organizations may be less than stellar in policing information, with a greater quantity of unsupported statements leaking through the regulatory sieve. Poor information may lead to decisions that increase spending on both ineffective and harmful drugs, as well as the health consequences of consuming them.

Harms caused by drugs may be addressed through the tort system. But FDA's current labeling authority, based on the current approval system, can affect whether manufacturers are or should be liable in tort. The next subsection explores how tort liability may change under the system and the costs of it doing so.

b. Liability

Patients injured by prescription drugs typically can assert claims against at least two potential parties. First, the manufacturer of the drug and, second, the physician that prescribed it.[216] Each standard of liability raises different legal and policy questions, though the upshot of both is a potential increase in costs associated with litigating tort claims.

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214. PAUL STARR, THE SOCIAL TRANSFORMATION OF AMERICAN MEDICINE 132–33 (1982).

215. *Id.* During this time, many "ethical" drugs were marketed along so-called "patent" medicines. *Id.* at 127. The distinction was drawn by the AMA, which viewed the former as legitimate (and hence could be advertised to physicians) and the latter as illegitimate (and hence could be advertised to the public only). *See id.* at 127–28.

216. Other potential parties include the hospital or health systems at which the physician works.

i) Product Liability for Manufacturers

Drug manufacturers can be liable under tort, contract, or other state laws for harms caused by a defect in a drug's manufacturing, design, and marketing in tort and similar theories under contract or other state laws.[217] Despite the potential state tort and contract claims against manufacturers, the defense of preemption can act as an effective bulwark against liability. Preemption, which derives from the Supremacy Clause of the Constitution, holds that federal law displaces state law in certain cases—most relevant here when they conflict.[218] Because courts have held that state law conflicts with federal law when it requires additional warnings or testing, the Federal Food, Drug, and Cosmetic Act ("FDCA") preempts a large variety of state law claims against drug manufacturers.[219] For generic manufacturers, recent case law suggests that nearly all claims against them, except those based on manufacturing defects, are preempted.[220] For brand manufacturers, the story is more complicated, with manufacturing, failure to warn, and even some design defect claims not preempted, though there is significant variation among courts.[221] What is clear, however, is that preemption leaves open a window for some claims that allege the manufacturer failed to update labeling to include new risk information.[222]

Although the doctrine now plays a central role in drug litigation,[223] it was not raised much as a defense to claims against drug manufacturers until after 1992, when the Supreme Court opened the door for a preemption defense in *Cipollone v. Liggett Grp., Inc.*[224] This shift may be explained by changes in tort doctrine that made it easier to prove liability for product defects (both in negligence and strict liability). Or it may simply have represented a larger shift in Supreme Court preemption jurisprudence.[225] Whatever the reason, existing preemption jurisprudence is premised on the depth and rigor of FDA

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217. David A. Simon, *Off-Label Preemption*, 2024 WIS. L. REV. 1079, 1085.

218. *Id.* at 1099.

219. *See id.* at 1110–11.

220. For possible exceptions, see *id.* at 1098–123, 1102 n.107.

221. *See id.* at 1098–101.

222. *Id.* at 1108.

223. For the development of the preemption doctrine in the context of the FDCA, see Mary J. Davis, *The Battle Over Implied Preemption: Products Liability and the FDA*, 48 B.C. L. REV. 1089, 1111–29 (2007).

224. 505 U.S. 504, 516 (1992); *see* David C. Vladeck, *Federal Preemption of State Tort Law: The Problem of Medical Drugs and Devices*, 33 PEPP. L. REV. 95, 106 (2005); Catherine M. Sharkey, *Drug Advertising Claims: Preemption's New Frontier*, 41 LOY. L.A. L. REV. 1625, 1625 (2007).

225. *See* Davis, *supra* note 223, at 1120–24.

review.[226] If FDA review becomes less rigorous, it is unclear how tort law will or should respond.

On the one hand, tort law may shrug its shoulders and point out that the "new" safety requirement ferrets out the same kinds of risks as the "old" review. Courts might reason that the crucial difference between the current and safety-only review is the lack of an efficacy requirement. Because the relevant difference in review does not relate to safety, preemption should bar similar claims under both regimes.

On the other hand, this kind of reasoning rests on the assumption that the "safety" review would be identical, or at least sufficiently similar, in each system. But that assumption is suspect. Phase I, II, and III studies do not and cannot identify all risks.[227] And while Phase III studies are designed primarily to assess efficacy, they also are designed to capture and evaluate some safety risks that may not have appeared previously.[228] The idea that efficacy studies add no value to safety is therefore misplaced.

This observation also helps to focus on the core of existing preemption jurisprudence, which is based on thoroughness of review.[229] Reduced rigor of *ex ante* review suggests a larger role for *ex post* state law regulation through litigation. The "long and arduous process" of obtaining approval will be replaced by something shorter and, while not sweet, perhaps less arduous.[230] In such cases, allowing tort law to pick up the slack of FDA regulation would help to constrain manufacturers when deciding which drugs to market and how.[231] Preemption decisions will likely be colored by this change, perhaps

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226. *See* Simon, *supra* note 217, at 1098–113.

227. U.S. FOOD & DRUG. ADMIN., GUIDANCE FOR INDUSTRY: PREMARKETING RISK ASSESSMENT 6 (2005), https://www.fda.gov/media/71650/download [https://perma.cc/742M-ASKT] ("[E]ven for a product that is rigorously tested preapproval, some risks will become apparent only after approval, when the product is used in tens of thousands or even millions of patients in the general population.").

228. *Id.* at 10 ("Broadening inclusion criteria in phase 3 enhances the generalizability of safety (and efficacy) findings.").

229. *See* Simon, *supra* note 217, at 1086; David A. Simon et al., *Innovating Preemption or Preempting Innovation?*, 119 NW. U. L. REV. 137, 144 (2024).

230. Seife v. U.S. Food & Drug Admin., 43 F.4th 231, 243 (2d Cir. 2022) (describing drug development); *accord* Jenkins v. Medtronic, Inc., 984 F. Supp. 2d 873, 882 (2013) (noting that a medical device underwent an "arduous premarket approval process"); *In re* Orthopedic Bone Screw Liab. Litig., 159 F.3d 817, 819 (3d Cir. 1998) ("[P]remarket approval is an arduous and time-consuming process; each submission requires an average of 1,200 hours of FDA review.").

231. Aaron D. Twerski, *The Demise of Drug Design Litigation: Death by Federal Preemption*, 68 AM. U. L. REV. 281, 295 (2018). Fundamentally this is a shift from *ex ante* to *ex post* regulation. But it is also a different *kind* of regulation. Tort law is not interested, necessarily, in efficacy. And part of the problem with this change may be to place judges and juries in a position to judge safety-efficacy tradeoffs and risks.

leading to a reduced preemptive effect. A more practical view, one consonant with preemption and drug regulation historically, would be to broadly allow state law claims. Federal law, in other words, should probably not preempt most claims.

An approach that focused on *ex post* risk evaluation may be more costly (and less efficient) than one that identifies them *ex ante*. Without (expansive) preemptive effect or rigorous FDA review, tort claims may impose new costs borne by patients, litigants, the court system, the health system, and the social welfare system.[232] The costs are not just the injuries that otherwise would have been prevented by the existing review, but also all the associated expenses related to them, including litigation, continued medical care and monitoring, and potential reliance on the social safety net (if patients are disabled or are already on public insurance).

This is particularly troubling given that increased speed to market may be associated with more adverse events,[233] and some quite severe ones at that.[234] This suggests that if comparative benefits of speedier approval are not significant, the costs could be mitigated by "improvements in both the monitoring and the communication of new-drug risks to physicians and patients."[235] Monitoring and communication, of course, are additional costs, and one with uncertain returns given the potential severity of adverse events.

More adverse events, particularly serious ones, can impose reputational costs on the FDA, potentially decreasing public trust in drug approval and leading consumers to seek alternative unproven methods of treatment that undergo no review whatsoever. Both consequences could increase the cost of drug development, drive investment away from drug development, and offset potential gains from lowering approval standards.[236]

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232. *See* Mary K. Olson, *Pharmaceutical Policy Change and the Safety of New Drugs*, 45 J.L. & ECON. 615, 617, 639–40 (2002). *But see* Michael A. Friedman et al., *The Safety of Newly Approved Medicines: Do Recent Market Removals Mean There Is a Problem?*, 281 J. AM. MED. ASS'N 1728, 1734 (1999).

233. *See* Olson, *supra* note 232, at 618. Another study that looked at a longer time period post user-fee amendments, however, found no evidence of such association. *See* Henry Grabowski & Y. Richard Wang, *Do Faster Food and Drug Administration Drug Reviews Adversely Affect Patient Safety? An Analysis of the 1992 Prescription Drug User Fee Act*, 51 J.L. & ECON. 377, 401 n.44 (2008).

234. Olson, *supra* note 232, at 616–17.

235. *Id.* at 640.

236. Eliminating or curbing tort claims through Congressional action would not necessarily offset gains of less litigation. Without liability, manufacturers may seek approval for drugs that have greater risks—or engage in promotional activity that accentuates drug risks.

Assessing the costs and benefits for either approach to preemption is difficult. And this choice is just one choice about liability of manufacturers. Another relates to liability of physicians.

ii) Liability for Physicians

In the context of prescription drugs, manufacturers ordinarily do not have a duty to warn consumers directly of the risks of the products. Under the so-called learned intermediary doctrine, manufacturers can satisfy this duty by warning the patient's prescribing physician.[237] This doctrine therefore limits manufacturer liability to situations where it failed to warn the physician of a particular risk, the physician would not have prescribed the drug had she known of the risk, and the risk materialized, causing injury to the patient. Practically, it means that claims against manufacturers are premised on the manufacturer's failure to warn the physician, not the patient.[238]

Physicians, however, can be liable when they commit negligence, including by prescribing, administering, or using a drug. A customary, rather than objective, standard governs physician negligence.[239] Using this standard, physicians can be liable for two types of claims.[240] One is a *knowledge* claim: the physician did not have adequate knowledge of the drug or its effects. The other is a *transmission* claim: the physician did not adequately inform the patient of the drug's potential effects.

Changing the standard of approval could drastically alter how tort law conceptualizes and applies negligence. Currently, liability is unlikely based on the transmission claim for both on- and off-label uses.[241] Informed consent

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237. Hill v. Searle Lab'ys, 884 F.2d 1064, 1070 (8th Cir. 1989). There are three narrow exceptions to the learned intermediary doctrine. One is mass vaccination campaigns. *See, e.g.*, Davis v. Wyeth Lab'ys, Inc., 399 F.2d 121, 130–31 (9th Cir. 1968). Another is prescription intrauterine devices for contraception. *See, e.g.*, *Hill*, 884 F.2d at 1070–71. The final exception, which only New Jersey currently recognizes, applies to drugs advertised directly to consumers. *See* Perez v. Wyeth Lab'ys Inc., 734 A.2d 1245, 1256–58 (N.J. 1999); *see also In re* Accutane Litig., 194 A.3d 503, 530–32 (N.J. 2018).

238. David A. Simon & Aaron S. Kesselheim, *Physician and Device Manufacturer Tort Liability for Remote Patient Monitoring Devices*, *in* DIGITAL HEALTH CARE OUTSIDE OF TRADITIONAL CLINICAL SETTINGS 109, 114–15 (I. Glenn Cohen et al. eds., 2024).

239. *See* Philip G. Peters, Jr., *The Quiet Demise of Deference to Custom: Malpractice Law at the Millennium*, 57 WASH. & LEE L. REV. 163, 165–170 (2000). The most recent published study on this issue suggests that the customary standard is actually the minority. *See id.* at 170, 187–88. But a more recent, forthcoming analysis calls this into question. Ani B. Satz & Liza Vertinsky, Customary Corruption 21–26 (Feb. 15, 2024) (unpublished manuscript) (on file with author).

240. David A. Simon, Off-Label Inducement 24–26 (Sept. 19, 2024) (unpublished manuscript) (on file with author).

241. Searches of Lexis and Westlaw revealed a total of less than thirty cases.

claims are usually fact specific and, for off-label uses, turn on various evidentiary presumptions courts have developed regarding the drug's approved labeling.[242] Turning from efficacy to safety, however, would place a greater burden on the physicians to know and understand the potential uses and risks of approved drugs. Increased knowledge requirements will increase demands on physicians to learn about new drugs. This could have the benefit of making physicians better informed, but it also increases information costs that would otherwise be defrayed by FDA review. Alternatively, physicians and attendant organizations may be poorly positioned to replace FDA, potentially raising liability costs.[243]

Transmission claims would also be more complicated to adjudicate. FDA labeling is likely to continue to exert some effect on the standard of care, but considerable uncertainty will surround the potential risks of a drug and what exactly a physician is required to disclose when prescribing or using it. While these uncertainties will eventually be settled, the increased burden on physicians—both in knowledge acquisition and transmission—will increase the costs of a safety-only system.

B. Benefits

The potential costs of implementing a new system are substantial, but so are the potential benefits. Like the previous Section, this Section identifies and highlights significant benefits rather than cataloging them all. It focuses on drug development costs; drug pricing, drug repurposing, and patents; public health research; access to drugs; data collection; and off-label prescribing.

1. Drug Development

One obvious benefit of the new system is that it will reduce the cost of bringing a drug to market. How much drug development costs fall will depend on the specifics of the system, including the type and quantity of evidence needed for reimbursement and the rules developed in tort to address harms caused to patients injured by prescription drugs. But at the very least, the system will allow companies to bring drugs to market and sell them without the same kind and quantity of data.

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242. *See* Simon, *supra* note 240, at 43.
243. *See* Ruger, *supra* note 121, at 2017.

2. Drug Pricing and Social Value

Reducing drug development is also likely to lower at least some drug prices, as firms pass along savings to consumers. But it also has the potential to alter the entire system of drug regulation by enabling pricing according to use. Pricing drugs according to use has two advantages over the current system. First, and most obviously, it allows tailoring pricing to *particular uses* rather than to *particular drugs*—what is typically referred to as indication-based pricing.[244]

Currently, remember, CMS pays for nearly all approved uses of approved drugs, and many off-label uses. Where it cannot or does not engage in some kind of evidence evaluation, it relies on private parties to limit use through utilization management strategies—an inefficient and often unreliable proxy to determine whether a use is worth paying for. Indication-based pricing allows CMS to pay different amounts for a drug according to how it is used.

Second, use-based reimbursement allows tailoring coverage and reimbursement decisions to the *social value* of particular uses—what is called value-based pricing.[245] While this pricing model might have many goals, the animating principle is that a firm's reward for drug innovation should be commensurate with the social value of the innovation.[246] In theory, it incentivizes firms to prioritize drugs that will provide the largest social benefit because those drugs will command the largest reward.[247] In turn, the public will spend more money on uses of drugs that provide greater social value than those that provide comparatively less social value.

For example, one might approximate the social value of the use of a drug by measuring the number of Quality Adjusted Life Years ("QALYs") the use is expected to add.[248] If a drug can be used to treat two conditions, X and Y, and the former produces one additional QALY and the latter seven, then the price of the drug for use Y should be worth something like seven times as much as the price for use Y. QALYs are by no means the only approach to estimating social value, and variations of this approach are not uncommon

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244. *See, e.g.*, Peter B. Bach, *Indication-Specific Pricing for Cancer Drugs*, 312 J. AM. MED. ASS'N 1629, 1629 (2014).

245. *See* Anna Kaltenboeck & Peter B. Bach, *Value-Based Pricing for Drugs: Theme and Variations*, 319 J. AM. MED. ASS'N 2165, 2165 (2018). In this case, the value-based pricing is also indication-based. *See id.* But indication-based pricing does not have to be value-based—it could be market-based, for example.

246. *See id.*

247. *See id.*

248. *See, e.g.*, Hemel & Ouellette, *Valuing Medical Innovation*, *supra* note 4, at 550–51; Kaltenboeck & Bach, *supra* note 245, at 2165.

among countries that adopt it.[249] While the new model expects pricing to match some value attributed to the use, it does not identify the precise value, or even the mechanism, one might use to set prices.

Pricing according to social value could be a potent weapon to reduce spending on "me-too" drugs and drugs that offer only marginal improvement over existing therapeutics while aligning innovation incentives to better meet the needs of society.[250] To be sure, the change is not costless. For example, this may increase the price of a drug for particular uses. But the benefits from those uses are justified by the concomitant social value provided by the use of the drug. And the price for uses with little social value will be reduced accordingly.

Despite this potential improvement, the effects of pricing frameworks on drug development are not perfectly predictable. And it is possible that social value pricing may be less effective than anticipated or that firms may find ways to manipulate it to generate profits without providing commensurate social value. Pricing, for instance, may take place through market forces, government fiat, or a negotiation process—and each may vary according to the metrics used to estimate and aggregate measures of social value. While each of these avenues may produce different drug prices, value-based pricing offers a way to anchor the price to some metric decided by factors other than simply demand or the manufacturer's ability to set a maximum price. For that reason, it provides a compelling, if imperfect, framework for pricing drugs.

What is more, this type of drug pricing could combat a current problem with accelerated approval—namely, that drugs come to market quickly but prices remain high after market entry.[251] For example, FDA recently granted accelerated approval to ELEVIDYS—a drug to treat muscle wasting that occurs in children with Duchenne muscular dystrophy—which the manufacturer priced at $3.2 million per dose.[252] CMS was its largest customer, though with discounts it paid "only" $2.56 million per dose.[253]

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249. *See* Claudio Jommi et al., *Implementation of Value-Based Pricing for Medicines*, 42 CLINICAL THERAPEUTICS 15, 19–21 (2020).

250. *See, e.g.*, Robin Feldman, *May Your Drug Price Be Evergreen*, 5 J.L. & BIOSCIS. 590, 617–18 (2018); Dmitry Karshtedt, *The More Things Change: Improvement Patents, Drug Modifications, and the FDA*, 104 IOWA L. REV. 1129, 1129–30 (2019).

251. *See* Bishal Gyawali & Aaron S. Kesselheim, *Reinforcing the Social Compromise of Accelerated Approval*, 15 NAT. REVS. CLINICAL ONCOLOGY 596, 596–97 (2018).

252. Steve Usdin, *Medicaid Will Be Biggest Payer for Sarepta's DMD Gene Therapy*, BIOCENTURY (June 23, 2023), https://www.biocentury.com/article/648416/medicaid-will-be-biggest-payer-for-sarepta-s-dmd-gene-therapy.

253. *See id.* Because the drug was approved for use in children, CMS paid for the drugs through Medicaid, not Medicare. While Medicare and Medicaid are different public insurance programs, CMS is the payor for both and both have similar off-label reimbursement frameworks.

While a therapeutic breakthrough for a terminal disease may be worth the high price, a recent confirmatory trial showed that this drug was not effective.[254] One might criticize CMS for having paid for an ineffective drug based on approval with limited evidence.[255] Leveling the criticism is even easier for other drugs that receive accelerated approval but do not undergo confirmatory studies at all or for long periods—leaving open both the government's pocketbook and the value proposition of the drug.

The new system mitigates this problem by allowing drugs to reach the market without any reimbursement guaranteed, lowering entry prices for drugs that would normally move through the accelerated approval pathway. Firms that want to provide more evidence of efficacy and social value can do so to generate higher payments.[256] CMS may even reconstitute the accelerated approval framework in a different form using better pricing metrics.

One version might, for instance, offer incentives for firms to participate in clinical trials (if initial evidence is strong enough)—perhaps by paying some multiple of what it would otherwise be willing to pay. Consider again ELEVIDYS, the muscular dystrophy drug, which under the new system likely would have reached the market sooner than under the accelerated approval pathway, and without the higher price tag. CMS could initially pay only a few thousand dollars per dose, for instance, instead of a few million, with a carrot of tens or hundreds of thousands of dollars if payments were made as part of a clinical trial or some systematic collection of data from patients.

Although combining a safety-focused approval regime with indication and value-based pricing might conceivably cut either way, it is reasonable to think that manufacturers will have at least some evidence of efficacy for a particular use prior to approval, and that those uses are likely to be more expensive than the ones that have no or weak evidence.[257] It is also reasonable to assume that firms will attempt to bring drugs to market for a variety of conditions and price-in consumers for those conditions where there is weak

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254. *See* Jason Mast & Adam Feuerstein, *Sarepta's Duchenne Gene Therapy Fails to Meet Primary Endpoint in Pivotal Trial*, STAT (Oct. 30, 2023), https://www.statnews.com/2023/10/30/sareptas-duchenne-gene-therapy-fails-to-meet-primary-endpoint-in-pivotal-trial.

255. The criticism is inapt insofar as the accelerated approval is designed to get more drugs to market faster, which will necessarily include ineffective drugs.

256. Social value and efficacy are linked. While all effective drugs will have social value, not all drugs will be equally effective. All things being equal, the more effective a drug, the more social value it has.

257. *See* Klein & Tabarrok, *supra* note 212, at 743–44, 768; Alex Tabarrok, *From Off-Label Prescribing Towards a New FDA*, 72 MED. HYPOTHESES 11, 12 (2009).

evidence of efficacy. Flexibility in pricing, then, is more likely than the current system to reduce deadweight loss associated with drug-based pricing.

3. Drug Repurposing: Patents and New Uses

Drugs have many potential uses, but under the current system firms often lack incentives to develop them. The problem is particularly acute for "unprotected" drugs—drugs that are not subject to some kind of protection, such as patent or regulatory exclusivities—for which pharmacy substitution laws and other regulations effectively eliminate any incentive to identify and develop new uses.[258]

The new system can potentially eliminate this problem by enabling firms to price discriminate based on use.[259] With institutional and technological methods of identifying infringers by prescribing software that requires diagnosis codes, firms will have a newfound ability to exclude others from new uses and, hence, to recoup their investment costs.[260] And because CMS (and presumably private insurers) will reimburse using evidence and not simply approval, the system encourages firms to develop evidence supporting a new use even if it does not incentivize the old-style efficacy approval of this use. Thus, by providing a mechanism to enforce new use patents and reimburse based on efficacy, the new system provides firms an incentive to patent and develop evidence of a new use's efficacy. And while not all new uses will have strong evidence, their value will be priced accordingly.

This could be a significant benefit. Drug repurposing is a promising strategy because it is cheaper than novel drug development from scratch.[261] Repurposing showed strong promise in the fight against COVID-19, and a variety of new therapeutic uses—such as using amitriptyline for pain and amantadine for Parkinson's Disease—have been discovered by using existing medications for an alternative purpose.[262] For drugs with high development

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258. Regardless of how convincing this critique, the evidence shows that basically no firms file NDAs after patents expire. *See, e.g.*, Babak Sahragardjoonegani et al., *Repurposing Existing Drugs for New Uses: A Cohort Study of the Frequency of FDA-Granted New Indication Exclusivities Since 1997*, J. PHARM. POL'Y & PRAC., No. 14:3, at 6 (Dec. 4, 2023), https://www.tandfonline.com/doi/epdf/10.1186/s40545-020-00282-8 [https://perma.cc/S32M-4433].

259. Roin, *supra* note 180, at 17.

260. *See* Amy Kapczynski & Talha Syed, *The Continuum of Excludability and the Limits of Patents*, 122 YALE L.J. 1900, 1903 (2013).

261. *See* David A. Simon, *Off-Label Innovation*, 56 GA. L. REV. 701, 710 (2022). This may be true, though to a lesser degree, than in the current system since approval will require less evidence than the current standard requires.

262. *See id.* at 710, 721–22.

costs and low probabilities of success, such as oncology, repurposing generic drugs like aspirin, statins, metformin, and tricyclic antidepressants could significantly cut development times and drug cost.[263] The potential benefits of developing new therapies without the costs of finding and testing a new drug compound could potentially outweigh other costs associated with the new system.

Enabling use-based reimbursement has the potential to stimulate research into innovative uses that currently languish because firms lack incentives to develop them. Of course, it is impossible to know in the abstract the full weight of either the costs or benefits, but the new system's ability to incentivize repurposing raises the possibility of a significant benefit that should not be ignored.

4. Public Health Research

Unlike most developed countries, the United States does not fully socialize medicine. Without a centralized repository for claims and medical records, the government has limited data about how drugs are used and their effects. The problem is compounded by a rather thin monitoring and reporting system. Consequently, many innovative off-label treatments are not disseminated and prescribing patterns are difficult to monitor.[264] Tracking trends in public health and drug usage, including monitoring easily abused drugs like opioids, therefore tends to be difficult and require concerted public action, often at the federal and state levels.[265] Prescription tracking systems, for example, are implemented at the state level, making their implementation diverse and often varied.[266] The same is true of state laws requiring payors to report claims information to databases, which exist in twenty-one states.[267]

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263. *See* Linda Sleire et al., *Drug Repurposing in Cancer*, 124 PHARMACOLOGICAL RSCH. 74, 75–77, 79–80 (2017).

264. *See* Eric von Hippel et al., *Market Failure in the Diffusion of Clinician-Developed Innovations: The Case of Off-Label Drug Discoveries*, 44 PUB. POL'Y 121, 123 (2016).

265. *See generally*, Jennifer Oliva & Taleed El-Sabawi, *The "New" Drug War*, 110 VA. L. REV. 1103 (2024) (discussing The War on Drugs and "state prescription drug monitoring programs" (PDMPs) that are used to regulate prescription drug misuse); Jennifer D. Oliva, *Dosing Discrimination: Regulating PDMP Risk Scores*, 110 CALIF. L. REV. 47, 74–80 (2022) (noting the rise of PDMPs in response to growing governmental concerns about prescription drug misuse).

266. *See* Oliva, *supra* note 265, at 76, 81; Elizabeth M. Stone et al., *Implementation and Enforcement of State Opioid Prescribing Laws*, 213 DRUG & ALCOHOL DEPENDENCE 1, 1–2 (2020).

267. DOUGLAS MCCARTHY, STATE ALL-PLAYER CLAIMS DATABASES: TOOLS FOR IMPROVING HEALTH CARE VALUE, PART 2—THE USES AND BENEFITS OF STATE APCDS 2 (2020),

A system that reimburses based on use could help ameliorate these problems. By requiring diagnosis codes on all prescriptions (and potentially claims) and paying for uses rather than drugs, public health researchers and innovators could more comprehensively study trends in drug usage at lower cost. It could also be used to help understand adverse event reporting,[268] potentially launching initiatives to prevent harmful prescribing. While the richest data would likely be limited to CMS beneficiaries, state laws requiring private claims reporting would supplement this information.[269]

5. Access to Drugs

More stringent approval standards delay access to drugs that patients need. This is particularly acute in certain practice areas, like oncology or neurology, where patients die or deteriorate rapidly.[270] But delays in approval also tend to affect vulnerable patient populations, particularly those with emerging diseases like as HIV/AIDS.[271] With lower barriers to entry, manufacturers will develop some drugs for uses that they otherwise would not have developed.[272] Patients, theoretically, could access these drugs and other drugs sooner than current regulatory frameworks allow. How much sooner and on what terms are open questions.

Importantly, however, this access would not be coupled with the same price tag associated with accelerated approval. It could also be more robust and inclusive than the existing Expanded Access program at FDA, which enables patients to access investigational drugs "outside of clinical trials when no comparable or satisfactory alternative therapy options are available."[273] Reimbursement here, just as with any drug after approval, could

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https://www.commonwealthfund.org/sites/default/files/2020-12/McCarthy_State_APCDs_Part2_v2.pdf [https://perma.cc/W3TJ-LN4Z]. This data is accurate as of 2020.

268. This is particularly true if diagnosis codes are required on adverse event reports. Abbott & Ayres, *supra* note 181, at 404.

269. *See All-Payer Claims Databases*, AGENCY FOR HEALTHCARE RSCH. & QUALITY (Mar. 2017), https://www.ahrq.gov/data/apcd/index.html [https://perma.cc/HAF6-HMN3].

270. *See generally* David J. Stewart et al., *The Importance of Greater Speed in Drug Development for Advanced Malignancies*, 7 CANCER MED. 1824 (2018) (explaining that time from discovery to approval has increased for oncology drugs and that this has enormous costs for patients in life years).

271. *See* Grossman, *supra* note 119, at 698.

272. *See* Michael D. Greenberg, *Information, Paternalism, and Rational Decision-Making: The Balance of FDA New Drug Approval*, 13 ALB. L.J. SCI. & TECH. 663, 664 (2003) (calling these "phantom" drugs).

273. *Expanded Access*, U.S. FOOD & DRUG ADMIN. (Feb. 28, 2024), https://www.fda.gov/news-events/public-health-focus/expanded-access [https://perma.cc/MTU4-PLZ8].

provide an incentive to allow access in closely monitored settings, with CMS or even the manufacturer setting conditions for access.

6. Data to CMS

Current law does not require FDA to disclose data to CMS nor does it require manufacturers to provide information to CMS except as part of the price negotiation process for certain drugs.[274] And historically, when CMS made coverage decisions, it consulted publicly available data.[275] Under a new system, the scope of CMS's legal authority to "demand" data is an open question. Perhaps the new system will more closely resemble the information required under the drug negotiation process where refusal to provide information can hamstring reimbursement decisions; perhaps it will be different, with CMS's ability to demand additional data adjusted upward or downward.

Whatever form the new system takes, it will require CMS to make coverage and reimbursement decisions based on more detailed review of the data than it currently has. And, to make the system effective—to make drug pricing actually reflect data regarding efficacy—it will need and likely have some power to demand data, whether de facto or de jure. Having more complete and robust data should enable more thoughtful and precise reimbursement determinations. This is particularly important in light of CMS's reconceptualized role as regulator of drug use.

Like with all of the potential benefits discussed so far, this one comes with costs, including the expanded role of CMS and the transaction costs of providing data. But there is at least reason to think that the costs applicable to any viability assessment are the same across benefits, and the changes may produce a multitude of benefits that outweigh these additional costs.

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274. *See* Inflation Reduction Act of 2022, Pub. L. No. 117-169, § 1191, 136 Stat. 1818, 1833–36 (codified at 42 U.S.C. §1320f).

275. A party requesting a National Coverage Determination can also submit articles, which CMS will review. *See, e.g.*, *Allogeneic Hematopoietic Stem Cell Transplantation (HSCT) for Myelodysplastic Syndrome*, CTRS. FOR MEDICARE & MEDICAID SERVS. (Aug. 4, 2010) (describing how CMS evaluates evidence, including a literature search and articles submitted by the requester). CMS may conduct a "technology assessment" to research an issue if it is particularly complex or the literature voluminous. *Factors CMS Considers in Commissioning External Technology Assessments*, CTRS. FOR MEDICARE & MEDICAID SERVS. (Apr. 11, 2006), https://www.cms.gov/medicare-coverage-database/view/medicare-coverage-document.aspx?MCDId=7 [https://perma.cc/7488-LJSK].

7. Limiting Harmful Prescribing

Another benefit of the new system is its ability to curtail off-label prescriptions that lack sufficient evidentiary support. Although off-label use can be necessary and therapeutic, it can also be harmful. The literature is replete with claims, sometimes overbroad, about off-label use being less safe than on-label use.[276] To the extent that off-label uses occur with weak evidence, however, it is driven by two informational deficits.[277] First, physicians lack adequate information about the evidence supporting the off-label uses. Second, insurers lack information about the prescribed use—they do not know the use for which a doctor is prescribing a drug.

When physicians lack information, it may lead to harmful or wasteful off-label prescribing. Physicians may prescribe drugs thinking they will help a patient when they will not. The problem is exacerbated by drug manufacturers that promote off-label uses.[278] The government's attempt to reduce this problem by regulating speech has faced legal challenges under the First Amendment.[279]

When payors lack information, however, they may deploy strategies to reduce off-label prescriptions. Because they do not know exactly why the drug is prescribed, they may adopt utilization strategies (formularies, tiering, and prior authorization) to reduce the *overall* prescriptions of a drug, regardless of the evidence supporting particular uses. This may lead to unduly restrictive payor practices, harming patients by limiting their access to drugs that have a valuable use. By reimbursing efficacious uses more generously than those with weak or no efficacy information, payors will also constrain physicians' ability to prescribe off-label, potentially stifling an important source of innovation.[280]

A new system could combat both problems. Because payors would have information about prescribed use, they could make reimbursement decisions based on the evidence for it rather than using utilization management to control expensive off-label use generally. Restricting coverage and

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276. *See, e.g.*, David C. Radley et al., *Off-Label Prescribing Among Office-Based Physicians*, 166 ARCHIVES INTERNAL MED. 1021, 1021 (2006); Nayoung Han et al., *Adverse Events Related to Off-Label Drugs Using Spontaneous Adverse Event Reporting Systems*, 17 THERAPEUTICS & CLINICAL RISK MGMT. 877, 877 (2021).

277. There are, of course, other factors that influence the likelihood a physician will prescribe off-label prescribing.

278. *See* Simon, *supra* note 217, at 1092–93.

279. *See* Simon, *supra* note 62, at 569–74.

280. The extent of this limitation will depend on the evidence of the use, the reimbursed amount, and the price of the drug to the patient.

reimbursement of certain uses would also signal to providers that the use does not have strong evidentiary support.[281]

Regulating off-label use through reimbursement also seems to avoid the First Amendment problems that arise when regulating off-label use through speech.[282] Prices signal information to physicians without necessarily restricting the speech of pharmaceutical firms.[283] Payors would spend less on ineffective or harmful medications, reducing costs to the health system. Patients, meanwhile, would be more likely to receive, and to benefit from, drugs that are effective.

One negative effect of this system is the erosion of the physician's autonomy and the harmful consequences that could follow. For example, a drug that has weak evidence for an off-label use may still be effective. In such cases, however, the harmfulness of limiting *coverage and reimbursement* would be offset somewhat by the patient's potential ability to access the drug through cash payment. If the drug has weak evidentiary support, it would likely be cheaper to obtain for that use.

IV. CONCLUSION

Some pro-market scholars have maintained that flipping the regulatory switch on efficacy from on to off would increase welfare by generating more drugs and quicker access to them. Public health scholars worry that turning off the lights on efficacy will hide safety issues and reduce incentives to produce effectiveness data. This Article argued that the approaches could be reconciled conceptually by using two switches, rather than one. The first, FDA approval, would turn on safety but leave efficacy off. The second, CMS, would turn on efficacy, but with a dimmer: reimbursement decisions would consider evidence of efficacy, modulating the probability that patients could access them. But because drugs would be more available and their access not determined by reimbursement, consumers would have quicker access to more drugs, though they would not always be willing and able to pay for them.

Despite the promise of this new lighting system, however, wiring it up reveals both new advantages and problems that can complicate the analysis.

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281. This would require providers to learn about the reimbursement rates of particular drugs. The private market could supply this information, or it could be communicated indirectly through insurance coverage decisions as to particular patients.

282. *See* Simon, *supra* note 62, at 569–74.

283. The extent to which FDA and the law generally constrain manufacturer speech will depend on questions explored in Sections III.A–B, *supra*. Even if those questions are resolved in a more speech-restrictive manner than under current law, the reimbursement signal would provide an additional source of information to physicians about the value of a use.

Turning out the lights on efficacy, for example, does more than simply relieve manufacturers from regulatory burdens; it also obscures a variety of costs, including those imposed by the interaction and integration with existing legal and regulatory frameworks. At the same time, however, adding the other regulatory switch to regulate efficacy through reimbursement has a variety of benefits that the shadow of the existing regime conceals. It may enable more tailored drug pricing regimes, reduce harmful off-label prescribing, and generate more information about drug use.

By illustrating the potential costs and benefits of this system, this Article has hopefully shown that lowering approval standards is not, as pro-market scholars often assume, an on–off switch. It requires careful thought about how divergent legal regimes, customized to a sprawling and comprehensive system of regulation, can or should accommodate changes to the existing landscape. These are not necessarily just questions about identifying costs and benefits, but also normative questions about what we ought to do, given the uncertainties involved in changing the system. Costs, of course, are not the only consideration, and the Article also hoped to show that there are benefits to altering the existing system that public health scholars may not have fully considered.

In the end, however, the uncertainty of both the costs and benefits counsels against a large-scale disruptive change to the existing framework. And, given that a complete cost-benefit analysis is probably "chimerical," our decisions about how to change the existing system should be premised on the scientific ideal underlying it. Specific potential changes should be identified through careful research. Those changes should be tested under controlled conditions. And the result of that research should be used to inform whether to implement the proposed change and, if so, in what form.