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Off-Label Speech

David A. Simon

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OFF-LABEL SPEECH

David A. Simon*

ABSTRACT

This Article argues that the Food and Drug Administration (“FDA”) should regulate drug manufacturer speech about off-label uses based on the evidentiary support for the relevant use. The more evidence that an off-label use is safe and effective, the less restrictive the regulation should be. The less evidence that an off-label use is safe and effective, the more restrictive the regulation should be. Although intuitive, this is not exactly how current regulation of off-label information works. If the FDA approves a drug, the manufacturer can advertise to doctors and patients for the approved indication. Drug manufacturers cannot, however, promote or provide information about an approved drug for an unapproved use—so-called “off-label” use—unless they fall within two narrow safe harbors. Yet many off-label uses are just as safe and effective as on-label (approved) ones. Other off-label uses are supported by quality clinical trial data even though they are not approved.

While the FDA recognizes that not all off-label uses are equally (un)supported by the same level of evidence, it has faced legal and practical challenges regulating information about them in a nuanced way. Courts have held unconstitutional the FDA’s regulations purporting to ban promotional off-label speech by drug manufacturers. And the safe harbors it has constructed are too shallow for much useful speech. To address these challenges, this Article

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proposes a new approach: working collaboratively with the Centers for Medicare and Medicaid Services, the FDA can use drug compendia—which identify, evaluate, and rate off-label uses—to create a graded system for regulating how drug manufacturers disseminate information about off-label uses that links informational restrictions to the level of evidence supporting the disseminated use. Not only does this system enable a flexible and evidence-based regulatory regime, it also can be easily designed to survive constitutional scrutiny.

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INTRODUCTION

Doctors need information about drugs. And drug companies are ready to give it to them. When the information concerns a use of a drug the Food and Drug Administration (“FDA”) approved, drug companies can promote their approved drugs to physicians.¹ Drug companies that want to provide information to physicians about an *unapproved* use of an approved drug, on the other hand, cannot do so except in limited circumstances.

There are two reasons why. The first is that unapproved uses of approved drugs—so-called off-label uses—often pose greater risks, both physically and monetarily, to patients than approved, on-label uses.² Because the FDA has not vetted unapproved uses, they may lack the evidentiary support enjoyed by their on-label counterparts. When drug companies promote off-label uses, they increase the probability that a physician will prescribe a drug off-label³—and, hence, increase the risk that the patient suffers harm from the unapproved use.

The second is that promoting off-label uses undermines the FDA approval process. Currently, a primary function of FDA approval is to incentivize firms

¹ Technically speaking, drugs are neither “approved” nor “approved for particular uses.” The FDA approves applications to market and sell new drugs in the United States, which include labeling that provides instructions for use under conditions for which the FDA has found the drug to be safe and effective. *See infra* Part I. For convenience, however, this Article employs the shorthand of “approved drugs,” “approved uses,” and “unapproved uses” (along with similar phrases).

² *E.g.*, David C. Radley, Stan N. Finkelstein & Randall S. Stafford, *Off-label Prescribing Among Office-Based Physicians*, 166 ARCHIVES INTERNAL MED. 1021, 1025, 1026 (2006) (estimating around 20% of all prescriptions were off-label). In some cases, it may even be the standard of care despite other on-label treatments.

³ *E.g.*, Bradley T. Shapiro, *Informational Shocks, Off-Label Prescribing, and the Effects of Physician Detailing*, 64 MGMT. SCI. 5925–44 (2018) (finding detailing increased probability of prescribing Seroquel off-label but arguing that overall detailing does not increase off-label prescribing); Anusua Datta & Dhaval Dave, *Effects of Physician-Directed Pharmaceutical Promotion on Prescription Behaviors: Longitudinal Evidence*, 26 HEALTH ECON. 450, 465–66 (2017) (finding detailing increases the probability of a physician prescribing the detailed drug). *But see* Ian Larkin, Desmond Ang, Jerry Avorn & Aaron S. Kesselheim, *Restrictions on Pharmaceutical Detailing Reduced Off-Label Prescribing of Antidepressants and Antipsychotics in Children*, 33 HEALTH AFFS. 1014, 1019–22 (2014) (finding that restrictions on off-label detailing at large academic medical centers reduced off-label prescribing of antidepressants and antipsychotics in pediatric patients).

to generate and disclose clinical trial data about a drug's safety and efficacy.⁴ If companies can promote drugs off-label once a drug is approved, they have little incentive to conduct clinical trials to obtain approval for off-label uses.⁵ Rather than spend large sums of money to conduct clinical trials for an uncertain result (an FDA approval determining a drug is safe and effective), drug companies can spend much smaller amounts for a sure thing (promote the off-label use and obtain additional sales *regardless* of safety/efficacy).

Yet many off-label uses are necessary and appropriate.⁶ For some patients, they are the only available treatment; for others, they represent the medically accepted "standard of care." Here, dissemination of off-label information can have positive, rather than negative, effects. By providing the physician information about a previously unknown treatment option, dissemination of off-label information increases the chance that a physician will prescribe a drug off-label to a patient who needs it. Limiting promotion of off-label uses, in this case, increases the risk that a physician will *not* prescribe a needed off-label treatment.⁷

In the FDA's view, the risk of too much off-label information outweighs the risk of too little. Despite the FDA's position that off-label drug promotion is

⁴ See Rebecca S. Eisenberg, *The Role of the FDA in Innovation Policy*, 13 MICH. TELECOMMS. & TECH. L. REV. 345, 370–71 (2007).

⁵ David A. Simon, *Off-Label Innovation*, 56 GA. L. REV. 701, 709–10 (2022).

⁶ One example of this is amitriptyline to treat neuropathic pain. *E.g.*, Joseph Acton, John E. McKenna & Ronald Melzack, *Amitriptyline Produces Analgesia in the Formalin Pain Test*, 117 EXPERIMENTAL NEUROLOGY 94, 94–95 (1992); Kalso Eija, Tasmuth Tiina & Neuvonen Pertti J., *Amitriptyline Effectively Relieves Neuropathic Pain Following Treatment of Breast Cancer*, 64 PAIN 293, 299, 300–01 (1995); R. Andrew Moore, Sheena Derry, Dominic Aldington, Peter Cole & Philip J. Wiffen, *Amitriptyline for Neuropathic Pain and Fibromyalgia in Adults*, COCHRANE DATABASE SYSTEMATIC REVIEWS., no. 12, 2012, at 15. *But see* Diana D. Cardenas, Catherine A. Warmis, Judith A. Turner, Helen Marshall, Marvin M. Brooke & John D. Loeser, *Efficacy of Amitriptyline for Relief of Pain in Spinal Cord Injury: Results of a Randomized Controlled Trial*, 96 PAIN 365, 371–72 (2002).

⁷ Sandra H. Johnson, *Polluting Medical Judgment? False Assumptions in the Pursuit of False Claims Regarding Off-Label Prescribing*, 9 MINN. J.L. SCI. & TECH. 61, 124 (2008) (arguing restricting off-label information can cause patient harm). This is not merely a theoretical argument simply because physicians seem to prescribe widely off-label and because off-label use can cause harm. *E.g.*, DAVID CAVALLA, OFF-LABEL PRESCRIBING—JUSTIFYING UNAPPROVED MEDICINE 153 (2015); Tewodros Eguale, David L. Buckeridge, Aman Verma, Nancy E. Winslade, Andrea Benedetti, James A. Hanley & Robyn Tamblyn, *Association of Off-Label Drug Use and Adverse Drug Events in an Adult Population*, 176 JAMA INTERNAL MED. 55, 58, 60 (2016) (Canadian study). Physicians may be prescribing the wrong drugs off-label, and other off-label drugs might work better. So, even if off-label prescribing was widespread and harmful, limiting off-label information could increase the risk that a patient does not receive a potentially helpful drug. At the same time, if improper off-label prescribing is widespread, then the answer is not necessarily to allow more off-label promotion. The correct response is to allow more information dissemination for better supported uses and less for poorly supported uses—exactly what this Article suggests.

illegal, however, courts have not been inclined to agree.⁸ Indeed, recent judicial decisions have called into question whether *any* prohibition on off-label promotion is constitutional.⁹

Responding to these judicial losses, the FDA has carved out safe harbors for manufacturer off-label speech.¹⁰ Unfortunately, these safe harbors are rather wooden and impractical. Drug manufacturers must provide an excessive amount of information in a format that is not useful to physicians. And there are few gradations on the kind, nature, and content of information drug manufacturers can provide if they fall within the safe harbors. *All* off-label uses that qualify for a safe harbor can be distributed in only the prescribed manner—a manner a physician is unlikely to find helpful.

Both of these challenges—the practical and the legal—are fundamentally about the quality and kind of evidence that supports an off-label use. When there is weak or no evidence supporting an off-label use, the risks posed by dissemination of off-label information are high. Restrictions on speech in such cases are likely to be constitutional because manufacturer statements about potential off-label uses are unlikely to be supported by evidence.¹¹ When strong evidence supports an off-label use, by contrast, the risks posed by dissemination

⁸ See *infra* Section I.B.1; see also *Schouest v. Medtronic, Inc.*, 13 F. Supp. 3d 692, 701–02 (S.D. Tex. 2014) (noting that when deciding whether the FDCA preempted state tort claims there is “statutory uncertainty on the question whether off-label promotion is *per se* unlawful,” declining to rule on whether bans on truthful off-label promotion violate the First Amendment, and holding that “federal law bars off-label promotion when it is false or misleading”); *United States v. Facticeau*, Criminal No. 15-cr-10076, 2020 WL 5517573, at *13–14 (D. Mass. Sept. 14, 2020) (upholding jury conviction on misbranding of a device based on jury instructions that explicitly stated that truthful, non-misleading speech cannot be used as the sole basis for a conviction, but that they can “constitute evidence of an intended use”); *Schuler v. Medtronic, Inc.*, No. CV 14–00241–R., 2014 WL 988516, at *1–2 (C.D. Cal. Mar. 12, 2014) (granting motion to dismiss various claims as preempted, including a state claim on off-label promotion, “[b]ecause federal law does not bar off-label promotion,” and, therefore, “off-label promotion cannot give rise to a state-law claim that is not preempted” (citing *United States v. Caronia*, 703 F.3d 149, 160 (2d Cir. 2012))); *United States v. Lebeau*, No. 10-CR-253, 2016 WL 447612, at *8–9 (E.D. Wisc. Feb. 3, 2016) (upholding conviction (by guilty plea) for misbranding where the substance in question could not be legally sold and thus failed *Central Hudson’s* first prong and noting the defendant made no arguments about the remaining three prongs). Scholars have dubbed the general deregulatory turn in free speech jurisprudence the “Lochnerization” of the First Amendment. *E.g.*, Amy Kapczynski, *The Lochnerized First Amendment and the FDA: Toward A More Democratic Political Economy, Response to the Columbia Law Review’s 2018 Symposium*, 118 COLUM. L. REV. ONLINE 179, 179–95, 198–200 (2018).

⁹ See *infra* Section I.B.1.

¹⁰ See *infra* Section I.A.2.

¹¹ As a matter of First Amendment jurisprudence, speech receives constitutional protection if it is not false or misleading. See *infra* Part I. Where speech is supported by more evidence, or there is not equivocal evidence, it is less likely to be misleading and more likely to be true. Beyond that threshold determination, however, the restrictions on constitutionally protected speech are more likely to be upheld if they are tailored to the evidence supporting the protected statement. The more closely the restrictions track the evidence of a particular statement, the more likely they are to be upheld by courts, as this Article argues in Section I.C.

of off-label information are low—and the risk of *not* disseminating enough information is high. Here, restrictions on off-label information dissemination are unlikely to be constitutional because manufacturer statements about potential off-label uses are likely to be supported by evidence. Put differently, restrictions on unsupported statements will be more likely to satisfy the constitutional test than will restrictions on supported statements.

Since both the legal and practical challenges of off-label promotion relate directly to the evidence supporting off-label uses, this Article argues that the best way to address them is to tie informational restrictions of off-label uses directly to the evidence base for the disseminated use.¹² Uses supported by strong evidence could be disseminated more than those supported by weak or no evidence.

To tie dissemination to evidence, this Article argues that the FDA, working with the Centers for Medicare and Medicaid Services (“CMS”), should regulate and use drug compendia: privately produced, publicly regulated publications that collect, evaluate, organize, and rate information about drugs. In this system, off-label uses with higher evidentiary ratings can be disseminated more freely than those with low ratings. The graded approach allows for regulations with a tighter fit to evidence, which, in turn, enables a greater flexibility in information dissemination activities. Because regulations will be tied directly to vetted evidence, the FDA can increase the kind and nature of information dissemination it allows.¹³ At the same time, it can limit these activities sufficiently to preserve traditional incentives for FDA approval.

¹² Generally speaking, this Article concerns off-label promotion of information that is not “healthcare economic information” (“HCEI”). 21st Century Cures Act, Pub. L. No. 114-255, § 3037, 130 Stat. 1033, 1105 (2016). The proposal—at least as described in Sections III.A.2–III.B.2—could, however, be adapted to regulate communication of HCEI. Because it is concerned with only *off-label* information, it does not address the myriad questions that might arise if the regime applied to both approved and unapproved uses. One reason for not applying this regime to both approved and unapproved uses is that it would fundamentally shift incentives for drug approval. Any system that graded evidence of approved uses would have to account for the effects that system would have on how much evidence companies would both need and want to generate to obtain FDA approval. That kind of proposal, while interesting, is beyond the scope of this Article.

¹³ In 2016, a working group of academics, attorneys, and medical professionals issued a report noting that this kind of a system could create a more nuanced system of regulation. GREGORY W. DANIEL, MORGAN H. ROMINE, JEFF ALLEN, NICHOLAS BAGLEY, AMY COMSTOCK RICK, COLEEN KLASMEIER, MARK B. MCCLELLAN, SARINA E. COATES, JOY LIU, PETER PITTS ET AL., POLICY OPTIONS FOR OFF-LABEL COMMUNICATION: SUPPORTING BETTER INFORMATION, BETTER EVIDENCE, AND BETTER CARE, DUKE-MARGOLIS CTR. FOR HEALTH POL’Y 10 (Feb. 2016), https://structurecms-staging-psyclone.netdna-ssl.com/client_assets/dwonk/media/attachments/56c6/61b7/6970/2d57/02bf/0000/56c661b769702d5702bf0000.pdf?1455841719 (“An approach that involves an outside reviewing body might also enable FDA to advance a model that more clearly differentiates between types and levels of communication, without modifying the FDA-approved product labeling. For example, the reviewing body might treat communication around off-label use

Linking information dissemination to evidence using compendia also enables the FDA to develop and use a new tool: a simplified and uniform disclosure document that can be included in manufacturer communications to physicians about off-label uses. This form—an example of which appears in the Appendix—effectively communicates to physicians complete and relevant information about evidence supporting an off-label use.

This approach not only solves the legal and practical problems with current regulation, but it also balances the two problems faced by public and private solutions posed by other scholars. Public-oriented solutions rely on a centralized authority, usually the FDA, to either conduct its own research or independently review evidence for off-label uses.¹⁴ Determinations about the evidence for a use could then inform decisions about whether promotional activities can occur. Because they fear *promotional false positives*—allowing promotion of uses that are not safe and effective—these proposals tend to overregulate at great expense, requiring significant government funding, gatekeeping, and administration.¹⁵

Private-oriented solutions, on the other hand, typically allow off-label dissemination once a private organization determines a particular use meets

that has become standard of care in a different manner than more tailored or less-well-established evidence on an off-label indication or within a specific patient subpopulation. Such a system could potentially play a more directed and focused ‘peer review’ alternative or supplement to the current role of peer-reviewed communications.”)

¹⁴ *E.g.*, *id.* at 8–11 (suggesting various approaches, including an informational resource maintained by the FDA that provides information about the evidence for particular uses and a “third-party”); Ryan Abbott & Ian Ayres, *Evidence and Extrapolation: Mechanisms for Regulating Off-Label Uses of Drugs and Devices*, 64 DUKE L.J. 377, 399 (2014); Aaron S. Kesselheim & Michelle M. Mello, *Prospects for Regulation of Off-Label Promotion in an Era of Expanding Commercial Speech Protection*, 92 N.C. L. REV. 1539, 1598–1601 (2014); Marc A. Rodwin, *Rooting Out Institutional Corruption to Manage Inappropriate Off-Label Drug Use*, 41 J.L. MED. & ETHICS 654, 655 (2013); George Horvath, *Off-Label Drug Risks: Toward a New FDA Regulatory Approach*, 29 ANNALS OF HEALTH L. & LIFE SCI. 101, 102–03, 127–28 (2020); *see also* David Kwok, *Controlling Excessive Off-Label Medicare Drug Costs Through the False Claims Act*, 27 HEALTH MATRIX 185, 219, 221 (2017).

¹⁵ *E.g.*, Kesselheim & Mello, *supra* note 14, at 1597–1603 (arguing that the FDA could expand its safe harbors using the FDCA’s advertising provision that allows advertising based on “substantial clinical experience” and “substantial evidence” standards); *see also* Fazal Khan & Justin Holloway, *Verify, Then Trust: How to Legalize Off-Label Drug Marketing*, 117 PENN ST. L. REV. 407, 431, 437–38 (2012) (proposing a system where the FDA would “verify” evidence about off-label uses, which could then be promoted); Tim Mackey & Bryan A. Liang, *Off-Label Promotion Reform: A Legislative Proposal Addressing Vulnerable Patient Drug Access and Limiting Inappropriate Pharmaceutical Marketing*, 45 U. MICH. J.L. REFORM 1, 37–41, 43–45 (2011) (proposing to allow off-label promotion for drugs to treat “vulnerable patient populations” upon application to, and approval by, the FDA, which “must revisit this categorization at least annually to account for changes in the makeup of these populations” and mandating information collection and disclosure); Brian A. Liang & Tim Mackey, *Reforming Off-Label Promotion to Enhance Orphan Disease Treatment*, 327 SCI. 273, 273–74 (2010) (proposing different off-label promotion schemes to disseminate knowledge of potential treatments for orphan diseases).

certain evidentiary requirements.¹⁶ Unlike their public-oriented counterparts, private-oriented proposals fear *promotional false-negatives*: not allowing promotion of uses that are safe and effective. As a result, these solutions are cheaper but lack enforcement and underregulate the conflicts likely to arise in a private market.

Using drug compendia to link information dissemination to the evidence supporting the disseminated use marries the best of both solutions—leveraging the efficiency benefits of private-oriented solutions with the oversight function of public-oriented ones. Because compendia are privately run, they have low administrative costs. But they are also subject to public regulation by the FDA and the CMS, which ensure that the process by which they evaluate and rate off-label uses is unbiased, reliable, and transparent.¹⁷ To the extent that promotional

¹⁶ Richard A. Epstein, *Against Permittis: Why Voluntary Organizations Should Regulate the Use of Cancer Drugs*, 94 MINN. L. REV. 1, 10–12, 19–20, 33–34 (2009) (arguing that, at least in the cancer context, people should be able to decide for themselves what treatments they accept as well as reject and that voluntary organizations, which he thinks should largely replace the FDA, are best equipped to help them decide); see also Jeffrey Chasnoff & Geoffrey Levitt, *Off-Label Communications: The Prodigal Returns*, 73 FOOD & DRUG L.J. 257, 272–74 (2018) (suggesting that we should apply “fundamental quality standards” to remedy off-label speech problems, noting that voluntary standards and resource on evidence for off-label use already exist in the form of “peer review, medical compendia, medical societies, and as a last resort, the courts applying a Lanham Act or other relevant legal regime”); John E. Osborn, *Can I Tell You the Truth? A Comparative Perspective on Regulating Off-Label Scientific and Medical Information*, 10 YALE J. HEALTH POL’Y L. & ETHICS 299, 340 (2010) (arguing for manufacturer self-regulation based on the British model); Daniel et al., *supra* note 13, at 10–11 (suggesting a third party could review evidence for off-label uses with FDA participation and make non-binding recommendations to guide FDA policy). But see Richard A. Merrill, *The Architecture of Government Regulation of Medical Products*, 82 VA. L. REV. 1753, 1798 (1996) (arguing that the view of the FDA as overly concerned with Type II Errors is simplistic).

¹⁷ The tight but elastic regulatory relationship is particularly important in light of renewed judicial interest in resurrecting the doctrine of private nondelegation, a subspecies of the more general constitutional doctrine of nondelegation. *Texas v. Comm’r of Internal Revenue*, 142 S. Ct. 1308, 1308–09 (2022) (Alito, J., joined by Thomas & Gorsuch, JJ., concurring in denial of certiorari) (agreeing with denial of a writ of certiorari based on a federal appeals court decision holding that the nondelegation doctrine was not violated, but stating “that this case presents an important separation-of-powers question” and “reluctantly incur[ring] in the denial of certiorari” because the relevant statute had been repealed and the relevant statute of limitations had lapsed). Traditionally, the nondelegation doctrine prevents Congress from giving away (delegating) its authority to the executive branch without providing sufficient guidance on how to exercise it (what is called an “intelligible principle”), *J.W. Hampton, Jr. & Co. v. United States*, 276 U.S. 394, 409 (1928), though this standard is exceedingly easy to satisfy. *E.g.*, *Gundy v. United States*, 139 S. Ct. 2116, 2129 (2019) (upholding limited delegation to U.S. Attorney General based on the intelligible principle rationale), *reh’g denied*, 140 S. Ct. 579 (2019). But a related concern can arise when Congress delegates its power to *private* entities. *E.g.*, *Ass’n of Am. R.R.s. v. U.S. Dep’t of Transp.*, 721 F.3d 666, 671–73 (D.D.C. 2013) (stating that “[e]ven an intelligible principle cannot rescue a statute empowering private parties to wield regulatory authority” because they are cabined by “the principle that private parties must be limited to an advisory or subordinate role in the regulatory process”), *vacated*, 575 U.S. 43 (2015); *Ass’n of Am. R.R.s.*, 575 U.S. at 60–62 (Alito, J., concurring); *id.* at 88–89 (Thomas, J., concurring in the judgment); *A.L.A. Schechter Poultry Corp. v. United States*, 295 U.S. 495, 541–42 (1935); *Carter v. Carter Coal Co.*, 298 U.S. 238, 311 (1936) (discussing both delegation and due process concerns raised by transfer of regulatory power to majority of market participants); *Sunshine Anthracite Coal Co. v. Adkins*, 310

false positives and negatives exist, they will result from bad evidence, not bad regulation. In short, using compendia to regulate dissemination of off-label promotion is likely to be cheaper than most public-oriented solutions and more effective than most private-oriented ones.

Compendia, though, have their own set of problems. Central among them are opacity, bias, and unreliability. Because these are significant problems, this Article does not propose using compendia in their current form. Instead, the FDA—working with the CMS—should regulate compendia directly and indirectly. Direct regulation specifies conditions, which, if met, would entitle a compendium to “recognized” status under current law. This includes uniform systems of (1) identifying, evaluating, and grading evidence; (2) identifying, evaluating, and acting on conflicts of interest and bias; and (3) publishing all information about (1) and (2). It could also entail additional compliance mechanisms that do not currently exist, including a requirement that compendia apply to “renew” their recognized status periodically and the audit or inspection of compendia by the CMS and/or the FDA. Because the CMS already has the statutory authority to regulate compendia this way—and because compendia are in need of reform—this aspect of the proposal is both practical and desirable.

Direct regulation, however, is not sufficient to link promotion to evidence. To do so, the FDA must regulate compendia *indirectly*. Currently the CMS indirectly regulates compendia by specifying what evidentiary ratings are

U.S. 381, 388 (1940); see *United States v. Article of Drug Ova II*, 414 F. Supp. 660, 665 (D.N.J. 1975) (questioning whether wholesale delegation of the definition of drug to a private compendium in the context of pregnancy tests violates the private nondelegation doctrine), *aff'd sub nom.* *United States v. Article of Drug Ova II*, 535 F.2d 1248 (3d Cir. 1976); see also Harold I. Abramson, *A Fifth Branch of Government: The Private Regulators and Their Constitutionality*, 16 HASTINGS CONST. L.Q. 165, 192 (1989) (“In private-delegation cases, the United States Supreme Court has further complicated nondelegation theory by failing to give careful attention to the crucial distinction between a delegation to a private actor and a delegation to a public one: the differences in their levels of accountability.”); James M. Rice, Note, *The Private Nondelegation Doctrine: Preventing the Delegation of Regulatory Authority to Private Parties and International Organizations*, 105 CALIF. L. REV. 539, 543 (2017).

The worry, of course, is that private entities that self-regulate are not subject to the same kind of public accountability as governmental agencies. Yet accountability concerns that drive arguments for extending the nondelegation doctrine to private actors—making such delegations per se unconstitutional—do not apply here. Regulation here is not *performed* by private entities; there is no self-regulation. Just like with drug approval and reimbursement, the *actual* regulators are existing federal agencies (the FDA and the CMS). And it is *regulation by these entities*, rather than a private company’s decision to rate a drug’s evidence as equivocal, which triggers the nondelegation. Moreover, it also seems unlikely that this kind of arrangement would violate either the due process clause or antitrust principles since the rating agencies do not compete with drug companies to produce or market drugs. And, finally, the FDA or the CMS can always decide compendia are no longer worth using and perform the function themselves.

sufficient to guarantee reimbursement.¹⁸ This Article proposes that the FDA do the same for purposes of information dissemination of off-label uses: it should specify the level of permissible information dissemination by reference to the evidence grade assigned for the disseminated use. Under this system, uses assigned high evidentiary grades could be disseminated with fewer restrictions than those assigned low evidentiary grades. Because compendia will not produce uniform assessments of evidence, this also gives the FDA flexibility in how it interprets the evidence base for a given use.

This Article proceeds as follows. Part I explains the current framework for regulating manufacturer speech about off-label uses. It highlights how the FDA's current approach to off-label information faces serious practical and legal challenges. It then argues that the best method for overcoming both of these obstacles is to link information regulation of off-label uses to the evidence supporting the use in question by relying on drug compendia. Part II explains drug compendia and their current weaknesses. Part III then reviews five different methods for using drug compendia to link the level of off-label information dissemination to the evidence base supporting that use. It argues that while drug compendia can provide this linkage, they need to be regulated more closely to do so effectively. After describing the proper nature and scope of this additional regulation, this Article illustrates how this proposal could work in practice using three examples.

I. THE FRAMEWORK AND CHALLENGES OF REGULATING INFORMATION ABOUT OFF-LABEL USES

The FDA regulates how drug manufacturers disseminate information about off-label uses for good reasons. But its regulations are not sensitive enough to the level of evidence supporting off-label uses. This Part explains the current regulatory framework, its deficiencies, and how it can be improved. Section A briefly explains how the FDA regulates the dissemination of information about off-label uses. Next, Section B explains why the current regulatory approach is practically and legally deficient. Section C concludes by arguing that a graded, compendia-based approach solves both the legal and practical problems that beset current FDA policy.

¹⁸ The CMS could, if it chose, set reimbursement rates based on the level of evidence supporting a given off-label use. Private payors often reimburse off-label uses at different rates depending on the use. *See infra* Section III.A.1.

A. *Regulating Off-Label Information: Prohibitions and Safe Harbors*

The FDA is a gatekeeper for prescription drugs. A new drug will not reach the market unless the FDA, after reviewing evidence a drug company provides, concludes that the drug is safe and effective for an “intended use.”¹⁹ If it approves a drug, the FDA does so as to a particular indication, dose, population, and method of administration. All of that information must appear on the drug labeling.²⁰

Drug companies can promote approved uses provided that the advertising conforms with the requirements of the Food, Drug, and Cosmetic Act (“FDCA”) and FDA regulations.²¹ Most notably, advertising must be for a drug’s “intended use.”²² Violating the FDCA can result in civil penalties and criminal prosecution.²³ Critically important to any prosecution under the FDCA, then, is how the person who markets the drug intends that it be used.²⁴ Evidence of intent is found by, among other things, looking at the drug’s labeling.

¹⁹ 21 U.S.C. § 321(g); 21 C.F.R. § 201.128 (2021) (defining “intended uses”); *id.* § 801.4 (2021) (defining meaning of “intended uses” on labeling). In 2015, the FDA proposed revising § 201.128 and § 801.4, which define “intended uses” to exclude the “knowledge” requirement in the regulations. But when the FDA finalized its regulations, it added a new requirement—“totality of the evidence.” 82 Fed. Reg. 2217, 2217 (Jan. 9, 2017). Met with resistance, the FDA delayed the amendment indefinitely. *Compare* Petition to Stay and for Reconsideration on behalf of Med. Info. Working Grp. (“MIWG”), Pharm. Rsch. & Mfrs. of Am. (“PhRMA”), and Biotechnology Innovation Org. (“BIO”), to Food & Drug Admin. (Feb. 8, 2017), <http://www.miwg.org/sites/default/files/Petition%20to%20Stay%20and%20for%20Reconsideration.pdf>, with 82 Fed. Reg. 2217 (Jan. 9, 2017) (detailing final regulation), *and* 82 Fed. Reg. 9501, 9501 (Feb. 7, 2017) (indicating regulation was delayed until March 21, 2017), *and* 82 Fed. Reg. 14319, 14319 (Mar. 20, 2017) (indicating regulation was further delayed until March 19, 2018), *and* 83 Fed. Reg. 11639, 11639 (Mar. 16, 2018) (indicating regulation was indefinitely delayed). Because of how drug laws developed historically, there are some unapproved drugs on the market. *E.g.*, 21 U.S.C. § 321(p).

²⁰ 21 U.S.C. § 355(b); 21 C.F.R. §§ 201.50, 201.55, 201.56, 201.57 (2021).

²¹ *See* U.S. DEP’T OF HEALTH & HUM. SERVS., FDA, CTR. FOR DRUG EVALUATION & RSCH. (CDER), CTR. FOR BIOLOGICS EVALUATION & RSCH. (CBER), CTR. FOR VETERINARY MED. (CVM) & CTR. FOR DEVICES & RADIOLOGICAL HEALTH (CDRH), GUIDANCE FOR INDUSTRY: PRESENTING RISK INFORMATION IN PRESCRIPTION DRUG AND MEDICAL DEVICE PROMOTION 3–4 (2009).

²² 21 C.F.R. § 201.100(d)(1) (2021).

²³ 21 U.S.C. §§ 331, 333(a) (specifying sanctions for violations of § 331); *see also id.* § 333(b) (specifying sanctions for marketing and advertising violations for prescription drugs).

²⁴ This does not mean that labeling is the *only* relevant information for determining whether an FDCA violation has occurred.

1. Prohibited Off-Label Information

Labeling, of course, exists only for drugs the FDA approves. Off-label uses are not approved, and the FDA uses this fact to regulate off-label information in four different ways.²⁵ The first two relate explicitly to drug labeling.

The FDA has construed “labeling” very broadly to include almost any written matter about the drug distributed by the manufacturer.²⁶ Written materials promoting off-label use, on the FDA’s reading, can violate the FDCA in two ways. First, the FDA can treat off-label promotion as introducing a “new drug”—one different from the approved use on the approved drug label.²⁷ The FDCA defines a new drug as one that is not “safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling.”²⁸ Since labeling is interpreted to include written off-label promotional materials, drug companies that use “written” communication to promote off-label uses are, in effect, “labeling” their drugs for unapproved uses—the statements are evidence of a new intended use. A manufacturer’s off-label promotions therefore introduces a “new drug”²⁹ without FDA approval,³⁰ expressly violating the FDCA.³¹

Second, off-label promotion may violate the misbranding provisions of the FDCA. Drugs are misbranded if their labeling is either “false or misleading in any particular,”³² or they fail to include “adequate directions for use.”³³ False or

²⁵ The FDA knows about and views these uses as legal. *See* Legal Status of Approved Labeling for Prescription Drugs; Prescribing for Uses Unapproved by the Food and Drug Administration, 37 Fed. Reg. 16503, 16503–04 (Aug. 15, 1972). The FDA published its most recent thinking on these issues in 2017. FDA, PUBLIC HEALTH INTERESTS AND FIRST AMENDMENT CONSIDERATIONS RELATED TO MANUFACTURER COMMUNICATIONS REGARDING UNAPPROVED USES OF APPROVED OR CLEARED MEDICAL PRODUCTS 1 (2017).

²⁶ 21 U.S.C. § 321(m); 21 C.F.R. § 202.1(l)(2) (2021). “Labeling” should be distinguished from “label.” The latter is defined narrowly to include only “a display of written, printed, or graphic matter *upon the immediate container of any article.*” 21 U.S.C. § 321(k) (emphasis added). The former, on the other hand, includes “all labels and other written, printed, or graphic matter (1) upon any article or any of its containers or wrappers, or (2) *accompanying such article.*” 21 U.S.C. § 321(m) (emphasis added).

²⁷ 21 U.S.C. § 321(p); 21 C.F.R. § 201.128 (2021) (defining “intended use”).

²⁸ 21 U.S.C. § 321(p)(1).

²⁹ *Id.* § 321(p).

³⁰ *Id.* § 355(b).

³¹ *Id.* § 331(d) (making it a violation of FDCA to introduce a new drug under 21 U.S.C. § 355); *id.* § 355(a)–(b) (requiring persons seeking to introduce a new drug to file a new drug application (“NDA”). New human drugs are exempt from § 352(f)(1) but only if the new drug has been approved under 21 U.S.C. § 355.

³² 21 U.S.C. § 352(a)(1).

³³ *Id.* § 352(f).

misleading drug labeling can be those that make literally false claims or therapeutic claims that are not substantiated by evidence.³⁴

Labeling can pass the false-or-misleading test and still fail the adequate-directions-for-use test, rendering the drug misbranded. “Adequate directions for use” means that the labeling must tell an ordinary person for what the drug should be used and how to use it safely for that purpose.³⁵ Drug companies can avoid the “adequate directions for use” requirement if drugs are sold on prescription and the requirement “is not necessary for the protection of the public health.”³⁶ To qualify for this exemption, a drug’s labeling must, among other things, provide “[a]dequate *information* for such use.”³⁷ But this requirement, in turn, mandates that the manufacturer specify how doctors can use the drug safely.³⁸ For new drugs, the information must be “the same in language and emphasis as,” and “consistent with and not contrary to,” the approved labeling.³⁹ For off-label uses, this is impossible because any off-label use is not an approved use. All such promotion can be used as evidence of an intended use inconsistent with the drug labeling, rendering a drug misbranded.⁴⁰

Beyond labeling, the FDA can prosecute claims of off-label promotion using its power to regulate drug advertising.⁴¹ If, however, the FDA uses the advertising provisions of the FDCA to regulate off-label promotion, it must

³⁴ Violators who misbrand or introduce a “new drug” without approval face civil penalties and potential jail time. *Id.* §§ 331, 333(a) (specifying sanctions for violations of § 331); *see also id.* § 333(b) (specifying sanctions for marketing and advertising violations for prescription drugs).

³⁵ 21 C.F.R. § 201.5 (2021).

³⁶ 21 U.S.C. § 352(f); 21 C.F.R. § 201.5 (2021) (defining adequate directions for use); *id.* § 201.128 (stating meaning of “intended uses” as referring to “objective intent” that can be discerned from “labeling claims, advertising matter, or oral or written statements by such persons or their representatives”).

³⁷ 21 C.F.R. § 201.100(d)(1) (emphasis added) (2021); *accord id.* § 201.100(a) (requiring drug be dispensed “in accordance with section 503(b),” which exempts drugs sold on prescription and authorizes FDA to promulgate regulations explaining conditions for exemption); PETER TEMIN, TAKING YOUR MEDICINE: DRUG REGULATION IN THE UNITED STATES 43–57 (1980) (explaining that the exemption arose out of the FDA’s shift, beginning with the 1938 Act, to designate drugs that must be sold on prescription and the exemption applied to drugs sold on prescription).

³⁸ 21 C.F.R. § 201.100(d)(1) (2021) (“Adequate information for such use, including indications, effects, dosages, routes, methods, and frequency and duration of administration and any relevant warnings, hazards, contraindications, side effects, and precautions, under which practitioners licensed by law to administer the drug can use the drug safely and for the purposes for which it is intended, including all conditions for which it is advertised or represented . . .”).

³⁹ *Id.*

⁴⁰ 21 U.S.C. § 352(f); *see infra* Section I.D.

⁴¹ 21 U.S.C. §§ 321, 331, 352, 355, 360b, 371; 21 C.F.R. § 201.100 (2021); *id.* § 202.1; *id.* § 314.81 (requiring in a post-marketing report a submission of specimen of labeling and advertisement “at the time of initial dissemination of the labeling and at the time of initial publication of the advertisement for a prescription drug product”).

classify the advertisements as not part of the drug labeling.⁴² Detailed regulations explain how drug companies can advertise their approved products.⁴³ Perhaps most importantly, these regulations require all drug advertisements to contain a “[t]rue statement of information . . . relating to side effects, contraindications, and effectiveness.”⁴⁴ A true statement of information is one that is not false, misleading, or lacks a fair balance between information about side effects/contraindications and effectiveness.⁴⁵ Any statement that is not a true statement of information violates the FDCA and expressly renders a drug misbranded.⁴⁶

What constitutes a statement of information that is false, misleading, or lacking fair balance is described by detailed regulations.⁴⁷ These statements fall into three categories. One is *substantiation* statements: those that are not supported by evidence.⁴⁸ A second is *selectivity* statements: those that are, in some way, supported by evidence but misleading because of how they are presented.⁴⁹ The final category, and the most relevant one for purposes of this Article, is *off-label* statements: those that claim or imply the drug can be used for an unapproved use.⁵⁰ Off-label statements include those that claim the “drug is better, more effective, useful in a broader range of conditions or patients,” or is safer than demonstrated by evidence;⁵¹ that “[u]se[] literature, quotations, or references” to suggest an off-label use;⁵² that suggest the drug is effective based on data “from patients treated with dosages different from those recommended in approved or permitted labeling”;⁵³ or that suggest that the drug is “safe and effective” for patients or diseases not captured by the label.⁵⁴

⁴² 21 U.S.C. § 352(n) (“This paragraph (n) shall not be applicable to any printed matter which the Secretary determines to be labeling as defined in section 321(m) of this title.”).

⁴³ 21 C.F.R. § 202.1 (2021).

⁴⁴ *Id.* § 202.1(e). *But see id.* § 202.1(e)(2) (exemptions).

⁴⁵ *Id.* §§ 202.1(e)(5)(i)–(ii).

⁴⁶ *Id.* § 202.1(k) (stating that violating the regulations constitutes misbranding); 21 U.S.C. § 331 (providing “[p]rohibited acts”); *id.* § 333 (providing “[p]enalties” for violating § 331); *id.* § 333(g) (providing penalties for “[v]iolations regarding direct-to-consumer advertising”).

⁴⁷ *Id.* § 202.1(e)(6).

⁴⁸ *Id.* §§ 202.1(e)(6)(i)–(iv), (xvi); *id.* § 202.1(e)(6)(vi) (can also be selectivity); *id.* § 202.1(e)(6)(xix) (can also be off-label).

⁴⁹ *Id.* §§ 202.1(e)(6)(v)–(vii), (xii)–(xv), (xvii)–(xviii), (xx).

⁵⁰ *Id.* §§ 202.1(e)(6)(i), (xi), (xix); *id.* § 202.1(e)(6)(xvii) (can also be selectivity).

⁵¹ *Id.* § 202.1(e)(6)(i) (stating the evidentiary standards as “substantial evidence or substantial clinical experience” which mirrors the new drug language in 21 U.S.C. § 321(p)).

⁵² *Id.* § 202.1(e)(6)(xi).

⁵³ *Id.* § 202.1(e)(6)(xvii) (but allowing “citation of reports of [such] studies”). This kind of statement is not, strictly speaking, an off-label statement unless it also implies or suggests the off-label dosage is effective.

⁵⁴ *Id.* § 202.1(e)(6)(xix).

The final way in which the FDA reaches off-label promotion is through what has been called the “squeeze play.”⁵⁵ This scenario arises when drug manufacturer speech constitutes neither “labeling” nor “advertising.” Often this occurs when sales representatives make oral statements about off-label use. Here, the FDA attempts to use its leverage over labeling and advertising to quash off-label promotional activities. It does so by classifying oral statements about off-label uses as evidence that a drug labeling did not provide “adequate information for use”—that is, as evidence that the defendant intended it to be used for a use other than the one on the label.⁵⁶ By incorporating these statements as evidence that a drug is misbranded, rather than looking directly to the labeling itself, the FDA extends its authority over off-label oral statements.⁵⁷

2. *Safe Harbors for Off-Label Information*

While the FDA purports to ban off-label promotion, it allows, through a guidance document (“FDA Guidance” or “Guidance”), manufacturers to disseminate off-label information in two limited circumstances.⁵⁸ Each of these exceptions is designed to allow evidence-based off-label communications by drug companies. Both exceptions, then, recognize that some off-label uses may be better supported than others. Despite that attempt, the safe harbors significantly constrain both the type of information and the manner in which drug companies can communicate it. They are, in other words, designed mostly to avoid promotional false positives—promotion of drugs that are not safe and

⁵⁵ PETER BARTON HUTT, RICHARD A. MERRILL & LEWIS A. GROSSMAN, *FOOD AND DRUG LAW: CASES & MATERIALS* 927 (4th ed. 2014); see Lars Noah, *Death of a Salesman: To What Extent Can the FDA Regulate the Promotional Statements of Pharmaceutical Sales Representatives?*, 47 *FOOD & DRUG L.J.* 309, 317, 326 (1992).

⁵⁶ 21 C.F.R. § 201.128 (2021) (explaining an “intended use[]” is determined by “objective intent[, which] may, for example, be shown by labeling claims, advertising matter, or oral or written statements by such persons or their representatives”).

⁵⁷ HUTT ET AL., *supra* note 55, at 931–33.

⁵⁸ Originally, the FDA had the statutory authority to ban these activities *unless* the manufacturer submitted a supplemental NDA (“sNDA”)—a formal application to the FDA to change the existing approved drug label, market a new dose or strength, or change the way it manufactures the drug. Food and Drug Administration Modernization Act (FDAMA), Pub. L. No. 105-115, §§ 401, 554, 111 Stat. 2296, 2356, 2359 (1997) (codified at 21 U.S.C. § 360aaa). But that provision sunset in 2006. Guidance for Industry on Good Reprint Practices for the Distribution of Medical Journal Articles and Medical or Scientific Reference Publications on Unapproved New Uses of Approved Drugs and Approved or Cleared Medical Devices; Availability, 74 Fed. Reg. 1694, 1694 (Jan. 13, 2009). In 2008, the FDA issued its guidance documents, which it finalized in 2009. *Id.* There is separate FDA guidance on communications with payors in light of statutory changes that allow more communication. Drug and Device Manufacturer Communications with Payors, Formulary Committees, and Similar Entities—Questions and Answers; Draft Guidance for Industry and Review Staff; Availability, 82 Fed. Reg. 6568, 6571 (Jan. 19, 2017); 21st Century Cures Act, Pub. L. No. 114-255, § 3037, 130 Stat. 1033, 1105 (2016) (codified at 21 U.S.C. § 352(a)).

effective. And, as this Article discusses in Section B, this raises practical and legal problems.

The first exception allows drug manufacturers to provide information about off-label uses in response to unsolicited requests for information.⁵⁹ A response must be specific to the request, and must be “truthful, balanced, non-misleading, and non-promotional scientific or medical information.”⁶⁰ Responses to solicited requests, by contrast, are “considered evidence of a [manufacturer’s] intent that a drug . . . be used for” an unapproved use.⁶¹ Drug companies that respond to solicited requests for off-label information are not covered by the safe harbor and can be prosecuted for misbranding or introducing a new drug.⁶² Worse, soliciting requests for off-label use *itself* may be a violation of the “FDA’s advertising and labeling regulations.”⁶³

Under the second exception, drug companies may distribute scientific articles, scientific/medical texts, and clinical practice guidelines provided they meet trustworthiness, form/format, content, and manner of distribution requirements.⁶⁴ The FDA imposes these requirements for all three categories of information (articles/reprints, reference texts, and clinical practice guidelines) covered by its Guidance, framing them throughout as dos (“should” or “must”) and don’ts (“should not” or “must not”).⁶⁵ While I have classified these requirements into four groups, the division is for analytical purposes only; often the requirements from one group bleed into another (e.g., some content

⁵⁹ See U.S. DEP’T OF HEALTH & HUM. SERVS., FDA, CTR. FOR DRUG EVALUATION & RSCH. (CDER), CTR. FOR BIOLOGICS EVALUATION & RSCH. (CBER), CTR. FOR VETERINARY MED. (CVM) & CTR. FOR DEVICES & RADIOLOGICAL HEALTH (CDRH), GUIDANCE FOR INDUSTRY: RESPONDING TO UNSOLICITED REQUESTS FOR OFF-LABEL INFORMATION ABOUT PRESCRIPTION DRUGS AND MEDICAL DEVICES 2 (Dec. 2011) [hereinafter FDA GUIDANCE: UNSOLICITED REQUESTS].

⁶⁰ *Id.* at 6.

⁶¹ *Id.* at 5.

⁶² See *id.* at 5–6; *infra* Section I.C.

⁶³ FDA GUIDANCE: UNSOLICITED REQUESTS, *supra* note 59, at 5 n.7. It is not clear if generating compendia addition requests by promoting to doctors qualifies as soliciting requests for information.

⁶⁴ See U.S. DEP’T OF HEALTH & HUM. SERVS., FDA, CTR. FOR DRUG EVALUATION & RSCH. (CDER), CTR. FOR BIOLOGICS EVALUATION & RSCH. (CBER), CTR. FOR DEVICES & RADIOLOGICAL HEALTH (CDRH), GUIDANCE FOR INDUSTRY: DISTRIBUTING SCIENTIFIC AND MEDICAL PUBLICATIONS ON UNAPPROVED NEW USES—RECOMMENDED PRACTICES 2, 7–17 (2014) [hereinafter FDA GUIDANCE: SCIENTIFIC & MEDICAL PUBLICATION] (updating the “FDA issued . . . guidance titled *Good Reprint Practices for the Distribution of Medical Journal Articles and Medical or Scientific Reference Publications on Unapproved New Uses of Approved Drugs and Approved or Cleared Medical Devices* (2009 guidance)”). The FDA does not describe these requirements as this Article has described them here. But, when analyzed, its guidance reduces to this Article’s description.

⁶⁵ See *id.* at 2.

requirements reflect concerns of trustworthiness). They are nevertheless useful tools to discuss the safe harbors and how the FDA Guidance is deficient.

a. Trustworthiness Requirements

The trustworthiness requirement aims to exclude information that may be biased or unreliable. When a manufacturer distributes journal articles, for example, the FDA wants those articles to meet certain quality, disclosure, funding, and truthfulness criteria.⁶⁶ These include publication by an independent organization with an independent expert editorial board and a publicly stated disclosure and conflicts of interest policy for all journal participants.⁶⁷ Peer-reviewed, published articles qualify,⁶⁸ while articles written by or at the request of manufacturers do not.⁶⁹ Certain kinds of articles also are categorically excluded.⁷⁰

Guidance for reference texts⁷¹ and clinical practice guidelines (“CPGs”) have similar trustworthiness criteria.⁷² The former must “[b]e based on a systematic review of the existing evidence,” published independently, and authored or edited by experts in the relevant subject area.⁷³ They also must be peer reviewed, be from a journal with accessible peer-review policies, and be sold in the normal course of trade (i.e., not specifically for purposes of distributing off-label information to physicians).⁷⁴

The latter (CPGs) are designed to help clinicians make decisions—and they are supposed to provide unbiased and complete information to help them do so.⁷⁵

⁶⁶ *Id.* at 7–10. *But see* Johnson, *supra* note 7, at 87–90 (reviewing evidence purporting to show industry bias and finding it inconclusive, and explaining that peer-reviewed journals have their own set of flaws that can result in negative outcomes because of incomplete information and publication biases).

⁶⁷ FDA GUIDANCE: SCIENTIFIC & MEDICAL PUBLICATION, *supra* note 64, at 7.

⁶⁸ *Id.*

⁶⁹ *Id.* at 9.

⁷⁰ *Id.* at 10.

⁷¹ *Id.* at 10–14.

⁷² *Id.* at 14–17. The IOM report briefly explains the history of clinical practice guidelines. *See generally* IOM REPORT, *infra* note 75, at 34–36.

⁷³ FDA GUIDANCE: SCIENTIFIC & MEDICAL PUBLICATION, *supra* note 64, at 11.

⁷⁴ *Id.*

⁷⁵ *See* INST. OF MED., COMM. ON STANDARDS FOR DEVELOPING TRUSTWORTHY CLINICAL PRAC. GUIDELINES, CLINICAL PRACTICE GUIDELINES WE CAN TRUST 1 (Robin Graham et al. eds., 2011) [hereinafter IOM REPORT] (“[Clinical practice guidelines] are able to enhance clinician and patient decision making by clearly describing and appraising the scientific evidence and reasoning (the likely benefits and harms) behind clinical recommendations, making them relevant to the individual patient encounter.”). *But see* Johnson, *supra* note 7, at 76–81 (noting CPGs have limited effect because they usually provide only general guidance, as the necessary data to develop more concrete, evidence-based guidelines are not available, and because of modes of

Perhaps for that reason—and perhaps because there are so many of them⁷⁶—they are subject to somewhat stricter trustworthiness requirements than reference texts. They must:

1. Be based on a systematic review of the existing evidence[;]
2. Be developed by a knowledgeable, multidisciplinary panel of experts and representatives from key affected groups[;]
3. Consider important patient subgroups and patient preferences[;]
4. Be based on an explicit and transparent (publicly accessible) process by which the CPG is developed and funded that minimizes distortions, biases, and conflicts of interest[;]
5. Provide a clear explanation of the logical relationships between alternative care options and health outcomes, provide clearly articulated recommendations in standardized form, and provide ratings of both quality of evidence and the strength of recommendations[; and]
6. Be reconsidered and revised when important new evidence warrants modifications of recommendations.⁷⁷

To comply with these requirements, the FDA suggests manufacturers consult the Institute of Medicine (“IOM”) report that produced them.⁷⁸ In it, they will find detailed descriptions of the standards by which these requirements can be met. Many of these standards are the same or similar to the requirements imposed on compendia, discussed below in Part II: a transparent funding policy, a conflicts of interest policy, systematic reviews of evidence, evidence rating systems, and constant revisions.⁷⁹ But there are also several others not required by compendia, such as patient input.⁸⁰

physician decision making); *see also* TEMIN, *supra* note 37, at 13, 88–90, 106–19 (explaining the “customary” model of decision making among physicians when choosing drugs).

⁷⁶ In 2008, the IOM found over 3,700 total clinical practice guidelines in the Guidelines International Network database, and 722 accepted guidelines by the NGC in that year alone. IOM REPORT, *supra* note 75, at 2.

⁷⁷ FDA GUIDANCE: SCIENTIFIC & MEDICAL PUBLICATION, *supra* note 64, at 14–15 (internal citations omitted); *accord* IOM REPORT, *supra* note 75, at 4–5.

⁷⁸ FDA GUIDANCE: SCIENTIFIC & MEDICAL PUBLICATION, *supra* note 64, at 14 & n.36, 15 n.38. The FDA guidance does not, however, specify that all the standards for trustworthiness in the report be followed, but its language strongly suggests they should be.

⁷⁹ IOM REPORT, *supra* note 75, at 6–9.

⁸⁰ *See infra* Part II.

b. Content Requirements

While trustworthiness requirements filter the kind of material that can be disseminated, content requirements explicitly describe what the disseminated information can convey. Articles, for example, must “[c]ontain information that describes and addresses adequate and well-controlled clinical investigations that are considered scientifically sound by experts with scientific training and experience to evaluate the safety or effectiveness of the drug.”⁸¹ They must also include “the approved labeling,” studies reaching different conclusions (if available), and “a comprehensive bibliography.”⁸² The information disseminated should also include “a prominently displayed and permanently affixed statement disclosing” the use included in the reprint, the fact that the use has not been approved by the FDA, known safety concerns (not discussed in the article(s)), and the financial interests implicated by the study.⁸³

Manufacturers also must not characterize the article as definitive or representative if that characterization is “inconsistent with the weight of credible evidence or if a significant number of other studies contradict conclusions set forth in the article.”⁸⁴ Nor can they make false or misleading statements or suggest the use of a product that is “dangerous to health when used in the manner suggested.”⁸⁵ Finally, the FDA also counsels against “attach[ing] [the article] to specific product information.”⁸⁶

Reference texts follow a similar pattern.⁸⁷ For full reference texts, the manufacturer must include a statement “prominently displayed and permanently affixed[,] . . . identifying the distributing manufacturer and disclosing that some of the uses for drugs and/or devices described in the reference text might not be approved or cleared by [the] FDA.”⁸⁸ It also must include a statement about financial conflicts and, in certain circumstances, the approved drug label itself.⁸⁹ Similar requirements apply to individual chapters of reference texts and CPGs.⁹⁰ Just as with scientific articles, the content of reference texts and CPGs cannot be false or misleading or suggest the product be used in ways that are unsafe.⁹¹

⁸¹ FDA GUIDANCE: SCIENTIFIC & MEDICAL PUBLICATION, *supra* note 64, at 7.

⁸² *Id.* at 7–8.

⁸³ *Id.* at 9–10.

⁸⁴ *Id.* at 8.

⁸⁵ *Id.* (citing 21 U.S.C. §§ 352(j), 321(m)).

⁸⁶ *Id.* at 9.

⁸⁷ *Id.* at 10–14.

⁸⁸ *Id.* at 10–11.

⁸⁹ *Id.* at 11–12.

⁹⁰ *Id.* at 12–13, 16–17.

⁹¹ *Id.* at 8, 13, 17.

c. Form/Format Requirements

Information that meets trustworthiness and content requirements also must take a particular form. In general, form requirements are concerned with how information is presented. For journal articles, manufacturers should distribute unabridged reprints/copies and a full representative publication reaching contrary results (if one exists).⁹² The supportive article “should not . . . [b]e marked, highlighted, summarized, or characterized by the manufacturer, in writing or orally, to emphasize or promote an unapproved use.”⁹³ And it should include the disclosures discussed above, which should be “permanently affixed” to the article.⁹⁴

Reference texts distributed in their entirety are permitted, provided they meet all other requirements.⁹⁵ If at least one chapter of the reference text discusses the off-label use at issue, the manufacturer must include the “approved product labeling” with the reference text.⁹⁶ When manufacturers distribute individual chapters of reference texts, however, the FDA imposes further formatting requirements.⁹⁷ The chapters must “[b]e unaltered/unabridged and extracted directly from the scientific or medical reference text in which [they] appear[.]”⁹⁸ Supportive unaltered/unabridged chapters should be included “[w]hen necessary to provide context.”⁹⁹ Both individual chapters and whole reference texts should include the necessary disclosure statement(s).¹⁰⁰ Manufacturers should not, just as with individual articles, “mark[], highlight[], summarize[], or characterize[]” them “to emphasize or promote an unapproved use”¹⁰¹ or attach reference texts to “specific product information.”¹⁰² Requirements for CPGs are almost identical to those for reference texts.¹⁰³

d. Manner of Distribution Requirements

When materials meet trustworthiness, content, and form requirements, information about off-label uses can be disseminated, but only in a certain

⁹² *Id.* at 7–8.

⁹³ *Id.* at 9 (emphasis omitted).

⁹⁴ *Id.* at 9–10.

⁹⁵ *Id.* at 10–12.

⁹⁶ *Id.* at 12.

⁹⁷ *Id.* at 12–13.

⁹⁸ *Id.* at 12.

⁹⁹ *Id.*

¹⁰⁰ *Id.* at 10–13.

¹⁰¹ *Id.* at 13.

¹⁰² *Id.* at 13–14.

¹⁰³ *Id.* at 14–17.

manner. Manufacturers can disseminate information—scientific articles, reference texts, and CPGs—but must do so separately from promotional materials.¹⁰⁴ Texts distributed by manufacturers at conferences “should not be distributed in promotional exhibit halls or during promotional speakers’ programs.”¹⁰⁵ Sales representatives who field questions that arise from distribution of information about off-label uses should direct questioners to a medical officer or department that is not part of the sales or marketing department.¹⁰⁶

B. Legal and Practical Challenges to the FDA Framework

Both exceptions—responses to unsolicited requests and distribution of scientific articles, reference texts, and CPGs—are considered “safe harbors.”¹⁰⁷ Operating within them protects manufacturers from FDCA prosecution. Even if manufacturers venture into more turbulent waters, though, doing so is not a per se violation of the law.¹⁰⁸ While this may seem obvious, it was not always the FDA’s position. And since it has been forced into that position by courts, it is worth noting the legal and practical challenges that remain for the Guidance.

1. Legal Challenges

The existing (2014) Guidance, discussed above, is not the FDA’s first foray into off-label regulation. It is based on a history, which includes previous

¹⁰⁴ *Id.* at 7–8.

¹⁰⁵ *Id.* at 8, 11, 15.

¹⁰⁶ *Id.*

¹⁰⁷ Prior guidance for continuing medical education and disseminating journal articles and reference texts, along with various provisions of the FDAMA had been successfully challenged in court. *Wash. Legal Found. v. Friedman (WLF I)*, 13 F. Supp. 2d 51, 74 (D.D.C. 1998), *amended by* 36 F. Supp. 2d 16 (D.D.C. 1999) (*WLF II*), *amended by sub nom.* *Wash. Legal Found. v. Henney (WLF III)*, 56 F. Supp. 2d 81 (D.D.C. 1999), and *vacated in part sub nom.* *Wash. Legal Found. v. Henney (WLF IV)*, 202 F.3d 331 (D.C. Cir. 2000). These cases held unconstitutional the guidance and statutory provisions penalizing certain forms of off-label promotion. *WLF II* limited the application of the permanent injunction in the original case, *WLF II*, 36 F. Supp. 2d at 20, and *WLF III* further amended the original order. *WLF III*, 56 F. Supp. at 87. *WLF IV* dismissed the FDA’s appeal but vacated the district court decisions. *WLF IV*, 202 F.3d at 337. For some reasons why the WLF court’s reasoning was flawed, see Kesselheim & Mello, *supra* note 14, at 1596.

¹⁰⁸ See *WLF I*, 13 F. Supp. 2d at 72–75. In *WLF I*, the district court issued an injunction with respect to the FDA’s written policies (and later provisions of the FDMA) on off-label promotion. *Id.* at 74. Although the court of appeals vacated the injunction based on the FDA’s change in legal posture, the FDA has agreed not to prosecute companies that engaged in off-label promotion within the terms of the injunction. See *WLF IV*, 202 F.3d at 335–37.

guidance from 1992,¹⁰⁹ 1996,¹¹⁰ and 1997.¹¹¹ All three pre-2014 guidance documents were superseded by the Food Drug Administration Modernization Act of 1997 (“FDAMA”)¹¹² and FDA regulations issued pursuant to it.¹¹³ Various provisions of the FDAMA permitted manufactures to disseminate information about off-label uses provided they met several requirements, including pre-distribution approval by the FDA¹¹⁴ and a certification that they would file (or that they actually file) an sNDA.¹¹⁵

History includes not just guidance documents and legislation, but also litigation about them. And shortly after the FDA released its 1992 guidance, the Washington Legal Foundation began mounting legal challenges with increasingly significant implications. What began as a citizen petition requesting that the FDA withdraw its 1992 guidance¹¹⁶ eventually morphed into a lawsuit that included not only the 1992, 1996, and 1997 guidance, but also the portions of the FDAMA that superseded them.¹¹⁷ When the entire legal battle ended in 2000, a federal district court had ruled as unconstitutional the relevant FDAMA provisions.¹¹⁸

Despite the ruling, the FDA managed to avoid the constitutional invalidation of the FDAMA (and its policy) on appeal—but only by abandoning its interpretation that the statute and its guidance documents constituted legal *requirements* rather than merely safe harbors.¹¹⁹ With the legal ground shifting underneath the FDA’s regulatory regime, it has tried to remain centered by

¹⁰⁹ Draft Policy Statement on Industry-Supported Scientific and Educational Activities, 57 Fed. Reg. 56412 (Nov. 27, 1992). The FDA also required preclearance for distribution of updates as early as 1991. *See* Brief for Appellee at *11, Wash. Legal Found. v. Henney, 202 F.3d 331 (D.C. Cir. 2000) (No. 99-5304).

¹¹⁰ Advertising and Promotion; Guidance, 61 Fed. Reg. 52800 (Oct. 8, 1996).

¹¹¹ Final Guidance on Industry-Supported Scientific and Educational Activities, 62 Fed. Reg. 64074, (Dec. 3, 1997).

¹¹² 21 U.S.C. §§ 360aaa–360aaa-6. The FDA promulgated implementing regulations in 1998. Dissemination of Information on Unapproved/New Uses for Marketed Drugs, Biologics, and Devices, 63 Fed. Reg. 64556, 64581 (Nov. 20, 1998) (to be codified at 21 C.F.R. pt. 99). These provisions of the FDAMA became effective “1 year after the date of enactment of [the] Act, or upon the Secretary’s issuance of final regulations pursuant to subsection (c), whichever [was] sooner.” Food and Drug Administration Modernization Act (FDAMA), Pub. L. No. 105-115, § 557(d), 111 Stat. 2296, 2364 (1997).

¹¹³ *WLF IV*, 202 F.3d at 334 n.4.

¹¹⁴ 21 U.S.C. §§ 360aaa(a)–(b).

¹¹⁵ *Id.* §§ 360aaa(a)–(b), 360aaa-3. The only way to avoid the sNDA requirement was to apply for and receive an exemption from the FDA showing that filing an sNDA would be “economically prohibitive” or “unethical.” *Compare id.* § 360aaa-3(d)(2)(A), *with id.* § 360aaa-3(d)(2)(B).

¹¹⁶ Citizen Petition Regarding the Food and Drug Administration’s Policy on Promotion of Unapproved Uses of Approved Drugs and Devices; Request for Comments, 59 Fed. Reg. 59820, 59820 (Nov. 18, 1994).

¹¹⁷ *See WLF IV*, 202 F.3d at 333–35 (summarizing the litigation).

¹¹⁸ Wash. Legal Found. v. Henney, 128 F. Supp. 2d 11, 15 (D.D.C. 2000).

¹¹⁹ *WLF IV*, 202 F.3d at 335; *Henney*, 128 F. Supp. 2d at 12–13.

gluing its feet to the floor. Immediately after the *WLF* case, the FDA issued a notice to “clarify” its position, classifying those same documents and statutory provisions as “safe harbors”: operating within them was not a violation of the FDCA, but venturing outside them could *potentially* lead to liability.¹²⁰

After the relevant FDAMA provisions sunset in 2006,¹²¹ the FDA issued new draft guidance documents,¹²² which it updated again in 2014 (discussed above in Section I.A.2).¹²³ The new guidance mirrored, and cemented, the shift caused by *WLF*: deviations from the guidance would not be considered per se violations of the law; they would be evidence of an objective intent to distribute a new or misbranded drug.

Although it sought stability in safe harbors, the FDA’s position remained vulnerable. A line of attack opened by *WLF* was followed by litigants successfully complaining that the FDA violated their First Amendment rights by regulating information about dietary supplements;¹²⁴ compounded pharmaceuticals;¹²⁵ physician prescribing patterns;¹²⁶ and, crucially, off-label

¹²⁰ That is, it could be used as evidence of intent to misbrand a drug or introduce a new drug without approval. *Compare* Decision in *Wash. Legal Found. v. Henney*, 65 Fed. Reg. 14286, 14286 (Mar. 16, 2000) (stating the statutory provisions and guidance materials regarding CME ruled unconstitutional in *WLF* “now constitute a ‘safe harbor’ for manufacturers that comply with them,” but that it would still consider enforcement for violations on a case-by-case basis), *with* Letter from Margaret M. Dotzel, Assoc. Comm’r for Pol’y, FDA, to Daniel J. Popeo & Richard A. Samp, *Wash. Legal Found.* (Jan. 28, 2002) (noting FDA would not likely initiate proceedings against manufacturers that complied with the injunction).

¹²¹ FDAMA, Pub. L. No. 105-115, § 557(e), 111 Stat. 2296, 2364 (1997) (providing provisions to sunset on the later of “September 30, 2006 or 7 years after the date on which the Secretary promulgates the regulations described in subsection (c),” which required the HHS to implement regulations for Sec. 551 within 1 year).

¹²² Guidance for Industry on Good Reprint Practices for the Distribution of Medical Journal Articles and Medical or Scientific Reference Publications on Unapproved New Uses of Approved Drugs and Approved or Cleared Medical Devices; Availability, 74 Fed. Reg. 8, 1694, 1694 (Jan. 13, 2009).

¹²³ FDA GUIDANCE: SCIENTIFIC & MEDICAL PUBLICATION, *supra* note 64, at 1–2.

¹²⁴ *Compare* *Pearson v. Shalala (Shalala I)*, 14 F. Supp. 2d 10, 17–22 (D.D.C. 1998) (holding that the FDA’s rules banning certain claims regarding dietary supplements did not violate the First Amendment because “[t]he FDA provided adequate reasons for adopting the standard and its decision was neither arbitrary nor capricious” and the “standard satisfied the *Central Hudson* test”), *rev’d*, 164 F.3d 650 (D.C. Cir. 1999), *with* *Pearson v. Shalala* 164 F.3d 650, 655–60 (D.C. Cir. 1999) (holding that the FDA’s rules banning certain *potentially* misleading health-related statements on dietary supplements failed *Central Hudson*’s test because, although the FDA’s interest was substantial, it failed to advance it either directly or through reasonable means), *and* *Pearson v. Shalala*, 130 F. Supp. 2d 105, 120 (D.D.C. 2001) (entering a preliminary injunction against the FDA’s attempt to ban the same statements as in *Shalala I* as unconstitutional because the claims at issue were not “inherently misleading” and because the FDA’s ban failed to advance the government’s substantial interest through reasonable means).

¹²⁵ *Thompson v. W. States Med. Ctr.*, 535 U.S. 357, 371–72 (2002) (determining speech of compounding pharmacies failed constitutional test under *Central Hudson*’s fourth prong).

¹²⁶ *Sorrell v. IMS Health Inc.*, 564 U.S. 552, 572, 577–78 (2011) (finding speech of pharmaceutical manufactures failed constitutional test under *Central Hudson*’s third prong).

uses.¹²⁷ The last of these blows—the Second Circuit’s decision about off-label uses in *U.S. v. Caronia*—was particularly crippling. It held that off-label promotion that is not false or misleading, by itself, fails to constitute misbranding.¹²⁸ What had been the FDA’s default position described only three years earlier (2009) in guidance documents was now in severe jeopardy—and many noticed.¹²⁹

Both decisions regarding information about off-label uses—*WLF* and *Caronia*—hinged on what has become the four-part First Amendment analysis from *Central Hudson Gas & Electric Corp. v. Public Service Commission of New York*.¹³⁰ First, the speech must concern a lawful activity and must not be misleading or false.¹³¹ Second, the government “must assert a substantial interest” to justify the restrictions.¹³² Third, the restrictions must directly advance the asserted interest.¹³³ Finally, “speech restrictions [must] be ‘narrowly drawn’” and “may extend only as far as the interest [the restrictions] serve[.]”¹³⁴

In *Caronia*, the court found that the government’s reading of the law—that drug manufacturers’ truthful statements about off-label uses can, by themselves, constitute misbranding—did not directly advance the substantial interest of protecting patients.¹³⁵ One reason was because the FDA did not prohibit off-label use; another related reason was that the FDA itself recognized the benefits of off-label use.¹³⁶ By inhibiting the ability of patients to realize the latter while

¹²⁷ *United States v. Caronia*, 703 F.3d 149, 162–63, 168–69 (2d Cir. 2012); see *United States v. Harkonen*, 510 F. App’x 633, 636 (9th Cir. 2013). Lower courts have dutifully followed the Second Circuit’s lead. *E.g.*, *Amarin Pharma, Inc. v. U.S. Food & Drug Admin.*, 119 F. Supp. 3d 196, 237 (S.D.N.Y. 2015) (granting preliminary injunction based on threatened FDA action to prosecute Amarin for misbranding using only truthful off-label promotion).

¹²⁸ *Caronia* left open the possibility that off-label promotion could be regulated if the statements about off-label uses *themselves* were false or misleading, something the government simply did not assert in *Caronia*. *Amarin Pharma, Inc.*, 119 F. Supp. 3d at 224–29; see also *United States v. Caputo*, 517 F.3d 935, 940 (7th Cir. 2008). *Caronia* did not foreclose the government’s ability to use promotional statements as evidence of misbranding. *United States ex rel. Polansky v. Pfizer, Inc.*, 822 F.3d 613, 615 n.2, 620 (2d Cir. 2016) (noting this in dicta when deciding a case under the False Claims Act).

¹²⁹ *E.g.*, Stephanie M. Greene, *After Caronia: First Amendment Concerns in Off-Label Promotion*, 51 SAN DIEGO L. REV. 645, 662–73, 707–08 (2014) (reviewing history of off-label decisions and arguing that the FDA has the authority to regulate off-label promotion after *Caronia*).

¹³⁰ 447 U.S. 557, 563–66 (1980).

¹³¹ *Id.* at 564.

¹³² *Id.*

¹³³ *Id.*

¹³⁴ *Id.* at 565 (quoting *In re Primus*, 436 U.S. 412, 438 (1978)).

¹³⁵ *United States v. Caronia*, 703 F.3d 149, 161, 166–67 (2d Cir. 2012).

¹³⁶ *Id.* at 166–67.

failing to prohibit the former, the FDA’s position did not advance the substantial government interest.¹³⁷

Failing to directly advance a governmental interest was not the law’s only defect. The ban on off-label promotion was also “more extensive than necessary to achieve the government’s substantial interests” because “[n]umerous, less speech-restrictive alternatives [were] available, as [were] non-criminal penalties.”¹³⁸ The court suggested a better approach might be to help doctors and patients figure out what was misleading by providing *additional* information.¹³⁹ Alternatively, it could use disclaimers or develop a graded system for distinguishing between drugs.¹⁴⁰ Subsequent district court decisions addressing these issues have not clarified the law.¹⁴¹

Using disclaimers alone to avoid the potential harms of off-label promotion is unlikely to succeed.¹⁴² But a more narrowly drawn regulation is both possible

¹³⁷ *Id.* at 167.

¹³⁸ *Id.*

¹³⁹ *Id.* at 168.

¹⁴⁰ *Id.* (“The government could develop its warning or disclaimer systems, or develop safety tiers within the off-label market, to distinguish between drugs.” (citing Coleen Klasmeyer & Martin H. Redish, *Off-Label Prescription Advertising, the FDA and the First Amendment: A Study in the Values of Commercial Speech Protection*, 37 AM. J.L. & MED. 315, 334 (2011))). The court suggested a few other methods as well, including “list[ing] all applicable or intended indications when” applying for approval, “creat[ing] . . . ceiling or caps on off-label prescriptions,” or having the FDA regulate or remind physicians of liability for off-label use. *Id.* For a discussion of off-label liability, see generally James M. Beck, *Off-Label Use in the Twenty-First Century: Most Myths and Misconceptions Mitigated*, 54 UIC J. MARSHALL L. REV. 1 (2021), and Simon, *supra* note 5, at 769.

¹⁴¹ Most of the cases discussing the legality of off-label promotion do so when analyzing whether the FDCA—specifically the Medical Device Amendments of 1976, § 2, 21 U.S.C. § 360k—which (expressly or impliedly) preempts some state law tort claims against *device* manufacturers. *E.g.*, *Houston v. Medtronic, Inc.*, 957 F. Supp. 2d 1166, 1179 (C.D. Cal. 2013) (noting in dicta, for the purposes of deciding the preemption of a fraud claim regarding off-label use, that “federal law forbids device manufacturers to promote any off-label uses, and certainly prohibits false or misleading off-label promotion”); *Ramirez v. Medtronic, Inc.*, 961 F. Supp. 2d 977, 990 (D. Ariz. 2013) (stating, in the context of analyzing express preemption, that “[o]ff-label promotion . . . violates federal law and may carry criminal penalties”); *Travelers Indem. Co. v. Cephalon, Inc.*, 32 F. Supp. 3d 538, 544 n.8 (E.D. Pa. 2014) (“[B]ecause a violation of the FDCA requires only prohibited off-label marketing, not fraudulent or deceptive conduct, this factual background is of limited value in alleging fraud.”), *aff’d*, 620 F. App’x 82 (3d Cir. 2015); *Hawkins v. Medtronic, Inc.*, 62 F. Supp. 3d 1144, 1151 (E.D. Cal. 2014) (noting that “[c]ourts appear split” on the issue of whether off-label promotion (of a device) alone constitutes misbranding); *Markland v. Insys Therapeutics, Inc.*, 270 F. Supp. 3d 1318, 1325 (M.D. Fla. 2017) (holding a state law claim as to a medical device as expressly preempted by the MDA and noting, in dicta, that “[w]hile it is not unlawful for a doctor to prescribe a drug for purposes other than those approved by the FDA, . . . it is generally accepted that a manufacturer’s off-label promotion of a drug runs afoul of federal law [as misbranding]” (citations omitted)), *aff’d*, 758 F. App’x 777 (11th Cir. 2018). Importantly, the MDA contains an express preemption provision that the drug provisions of the FDCA do not. 21 U.S.C. § 360k(a).

¹⁴² *E.g.*, Aaron S. Kesselheim, John Connolly, James Rogers & Jerry Avorn, *Mandatory Disclaimers on Dietary Supplements Do Not Reliably Communicate the Intended Issues*, 34 HEALTH AFFS. 438–46 (2015) (performing a meta-analysis and finding evidence supporting the thesis that disclaimers have little effect on

and beneficial. As this Article explains below, using a graded system to regulate off-label information based on the evidence base for the proposed use would satisfy constitutional requirements and also more closely track the policy objectives in regulating off-label speech. That, along with providing additional information, is what this Article proposes to do in Part III. Not only does this proposal offer the potential to regulate truthful off-label promotion, but it solves the problem that now bedevils jurisdictions where truthful off-label promotion is permissible: deciding what is false or misleading.¹⁴³

2. *Practical Challenges*

While the legal challenges to off-label regulation are serious—and this Article’s proposal addresses them—the FDA’s attempts to restrict off-label speech also face practical difficulties. Two are highlighted here. First, they are too rigid. As noted above, manufacturers can disseminate only three kinds of documents containing information about off-label uses (scientific articles, reference texts, and CPGs). And each of these must meet specific requirements about the trustworthiness, content, form, and manner of distribution. Doctors, however, generally do not even read drug *labeling*.¹⁴⁴ And much of their decision-making process follows a customary, rather than strictly “evidence-based,” model.¹⁴⁵ Sharply constraining off-label information, then, limits potentially useful information to doctors.

consumers of dietary supplements). This study did note it was limited in an important way: none of the studies it reviewed evaluated disclaimer effect on physicians. *Id.* at 440. But the authors argued that, based on prior research, they expected physicians to behave much like consumers. *Id.* None of the studies reviewed by the authors evaluated the effect of a disclaimer on prescription drugs, either. *Id.* The effectiveness of disclaimers has been questioned in other contexts as well. *E.g.*, Jacob Jacoby & George J. Szybillo, *Why Disclaimers Fail*, 84 TRADEMARK REP. 224, 237 (1994); Kesten C. Green & J. Scott Armstrong, *Evidence on the Effects of Mandatory Disclaimers in Advertising*, 31 J. PUB. POL’Y & MARK. 293, 302 (2012).

¹⁴³ See *Amarin Pharma, Inc. v. U.S. Food & Drug Admin.*, 119 F. Supp. 3d 196, 214–37 (S.D.N.Y. 2015) (extensively analyzing the parties’ disagreement about the necessary disclosures required by manufacturer then analyzing them as aiding in the determination of whether information was false or misleading when ruling to issue a preliminary injunction against the FDA); see also *Complaint at 3–4, Pacira Pharms., Inc. v. U.S. Food & Drug Admin.*, No. 1:15-cv-07055 (S.D.N.Y. Sept. 8, 2015) (arguing that the FDA Warning Letter claiming Pacira’s communication of off-label uses of their analgesic violated the First Amendment); *Settlement Agreement at 2–3, Pacira Pharms., Inc. v. U.S. Food & Drug Admin.*, No. 15-cv-07055 (S.D.N.Y. Dec. 15, 2015) (settling *Pacira* lawsuit and allowing for certain communications and noting that FDA withdrew its Warning Letter on October 13, 2015).

¹⁴⁴ *E.g.*, Donna T. Chen, Matthew K. Wynia, Rachel M. Moloney & G. Caleb Alexander, *U.S. Physician Knowledge of the FDA-Approved Indications and Evidence Base for Commonly Prescribed Drugs: Results of a National Survey*, 18 PHARMACOEPIDEMIOLOGY & DRUG SAFETY 1094, 1099 (2009) (finding that “physicians may lack adequate knowledge of the FDA-approved indications” based on a survey addressing common drug-indication pairs).

¹⁴⁵ See TEMIN, *supra* note 37, at 106–07.

Take, for example, the requirements of CPGs. Trustworthiness criteria limit the type of CPGs companies can distribute.¹⁴⁶ While each CPG may contain important information, not all drug uses are included in CPGs¹⁴⁷ and not all doctors read them. Very few even follow—some simply cannot follow—those they do read.¹⁴⁸ Yet doctors may benefit—in some cases doctors may need—information about a use even if that use is not included in a CPG. And they might not receive this information otherwise, even if it is contained in relevant literature (e.g., an article or series of scientific articles that qualify under the safe harbor). Constraining private companies’ ability to provide information to physicians, in these cases, has significant costs, including limiting treatment options, reducing information flow, and stifling innovative activity.¹⁴⁹

Rigidity is not the Guidance Documents’ only problem; they are also too vague. Many of the requirements discussed above give the impression that there are clear rules for evaluating evidence about off-label uses and, hence, dissemination of information about them. Take a seemingly simple requirement that the drug cannot be “dangerous to health when used in the manner suggested.”¹⁵⁰ This statement tells manufacturers only that dangerous off-label uses will be misbranded (a truism by statute), not what constitutes a use

¹⁴⁶ The IOM report recognizes that non-conforming clinical guidance can also have benefits. IOM REPORT, *supra* note 75, at 26 (“Although the committee recognizes that other forms of clinical guidance may have value, addressing them was beyond the scope of this report.”). This also includes both mandating additional information (e.g., to provide context and contrast it from the approved use) and prohibiting certain information or actions (e.g., highlighting or excerpting). *See id.* at 25–26.

¹⁴⁷ Florian Fischer, Kerstin Lange, Kristina Klose, Wolfgang Greiner & Alexander Kraemer, *Barriers and Strategies in Guideline Implementation—A Scoping Review*, 4 HEALTHCARE 36, 36 (2016) (“The criteria and prerequisites for developing guidelines are: a highly prevalent disease or frequently used medical procedure, high associated costs and current variations in practice.”); Robbie Foy, Graeme MacLennan, Jeremy Grimshaw, Gillian Penney, Marion Campbell & Richard Grol, *Attributes of Clinical Recommendations that Influence Change in Practice Following Audit and Feedback*, 55 J. CLINICAL EPIDEMIOLOGY 717, 717–22 (2002) (evaluating compliance and change among gynecologists in Scotland using retrospective audit along thirteen attributes of CPGs).

¹⁴⁸ This problem is a recurring one in the medical literature, and the reasons for non-adherence are varied. *E.g.*, Michael D. Cabana, Cynthia S. Rand, Neil R. Powe, Albert W. Wu, Modena H. Wilson, Paul-André C. Abboud & Haya R. Rubin, *Why Don’t Physicians Follow Clinical Practice Guidelines?: A Framework for Improvement*, 282 JAMA 1458, 1460–61 (1999) (surveying literature and finding “[a]dherence [b]arriers” related to “physician knowledge (lack of awareness or lack of familiarity), attitudes (lack of agreement, lack of self-efficacy, lack of outcome expectancy, or inertia of previous practice), or behavior (external barriers)” with external barriers including guideline-, environmental-, or patient-related factors); Jako S. Burgers, Richard P.T.M. Grol, Joost O.M. Zaat, Teun H. Spies, Akke K. van der Bij & Henk G.A. Mookink, *Characteristics of Effective Clinical Guidelines for General Practice*, 53 BRIT. J. GEN. PRAC. 15 (2003) (evaluating twelve attributes of guideline characteristics correlated with compliance using previous study data of 200 general practitioners in the Netherlands).

¹⁴⁹ Simon, *supra* note 5, at 739.

¹⁵⁰ FDA GUIDANCE: SCIENTIFIC & MEDICAL PUBLICATION, *supra* note 64, at 8 (citing 21 U.S.C. §§ 352(j), 321(m)).

dangerous to health. One might read this as the same standard the FDA would use to reject a drug application on safety grounds. If so, does this mean Phase 3 clinical trials must be completed? Phase 2? Or does it mean something else entirely? The Guidance Documents are unclear and case law is of little use.¹⁵¹ And given that all drugs have side effects, what kind of adverse events—the number and kind—are sufficient to make a drug dangerous? It is a problem the FDA has left for litigation.¹⁵²

Similar problems dog attempts to clarify content requirements. Under the FDA Guidance, manufacturers are prohibited from characterizing an article as representative “if it is inconsistent with the weight of credible evidence or if a significant number of other studies contradict the conclusions set forth in the article.”¹⁵³ But what constitutes the “weight of credible evidence” or “a significant number”? What if there are only two, conflicting studies? What if there are three studies, which all support the characterization but are of weak evidentiary value? What if there is a modestly sized randomized controlled trial that supports a marginal benefit for the use, but two smaller observational studies show a negative or harmful result? Does this mean that only off-label uses with sufficient safety data may be disseminated?¹⁵⁴

The trustworthiness criteria, too, suffer from vagueness. Any use included in a trustworthy CPG is fair game. And although CPGs incorporate evidence grades and recommendations, they do not necessarily do so uniformly. Unlike the process for regulating compendia, discussed in Part II, there is no longer a centralized authority that “recognizes” CPGs that conform to the criteria

¹⁵¹ Hardly any case law exists expounding the meaning of 21 U.S.C. §§ 352(j) and 321(m). *But see* Food & Drug Admin. v. Brown & Williamson Tobacco Corp., 529 U.S. 120 (2000) (21 U.S.C. § 352(j) case); United States v. Articles of Food & Drug, 444 F. Supp. 266 (E.D. Wis. 1978) (21 U.S.C. § 352(j) case); United States v. Lanpar Co., 293 F. Supp. 147 (N.D. Tex. 1968) (21 U.S.C. § 352(j) case); United States v. Undetermined Quantities of Cal-Ban 3000, 776 F. Supp. 249 (E.D.N.C. 1991) (21 U.S.C. § 321(g) case); Ass’n of Am. Physicians & Surgeons, Inc. v. U.S. Food & Drug Admin., 226 F. Supp. 2d 204 (D.D.C. 2002) (21 U.S.C. § 321(g) case). What little there is tells us virtually nothing about the meaning of the phrase in this or other contexts.

¹⁵² This may be a deliberate decision based on norms that have developed around off-label promotion. In other words, the Guidance Documents may have solidified into an informal understanding among drug companies about what the FDA permits and, by implication, what might rouse the FDA’s feathers. Even if this is true, however, the Guidelines can still be vague—because they leave open interpretive questions and the primary way to test new boundaries is by risking an FDA enforcement action.

¹⁵³ FDA GUIDANCE: SCIENTIFIC & MEDICAL PUBLICATION, *supra* note 64, at 8.

¹⁵⁴ A similar hitch hobbled the FDA when it tried to regulate health claims on dietary supplements. *Pearson v. Shalala*, 164 F.3d 650, 653–54 (D.C. Cir. 1999) (explaining FDA failed to explain how it measured “significant” scientific agreement or “otherwise defined the phrase”).

mentioned above.¹⁵⁵ This provides manufacturers with significant discretion to decide what is trustworthy. Because private companies are likely to select the CPG that best supports its use, the FDA must assess each individual CPG to pursue an enforcement action against private actors. This is a time consuming and difficult process.¹⁵⁶ Given the significant number of CPGs floating around,¹⁵⁷ it would be unreasonable to expect the FDA to police them except in cases of widespread violations.

Vagueness may seem like a problem. But it may actually be a design feature of the guidelines themselves. The FDA may simply be betting that manufacturers are risk averse. Vagueness here gives manufacturers both more latitude to act but also more potential risk. So, the thinking goes, vagueness actually promotes the FDA's efforts to limit off-label information. Because the regulatory structure is so rigid, it also results in overregulation to avoid promotional false positives. This is particularly true for off-label uses with limited or emerging evidence.

C. Solving Legal and Practical Challenges: Linking Information to Evidence

Because of these legal and practical challenges, this Article proposes a different kind of regulatory regime: link the kind, content, form, and quantity of off-label information dissemination to the evidence supporting each off-label use. A graded, evidence-based approach to off-label promotion would be consistent with the FDA's mission to regulate drugs based on safety and efficacy. The safer and more effective the use, the less restrictive the off-label regulations should be. The less safe and less effective the use, the more restrictive the off-label regulations should be. To link the information regulation to evidence, the FDA should use drug compendia, which evaluate and "grade" the evidence base for off-label uses.

This approach is fundamentally different from existing scholarship. Most scholars addressing this question have argued that the current judicial approach

¹⁵⁵ Until 2018, the National Guideline Clearinghouse ("NGC") *did* evaluate CPGs for inclusion. Susan Scutti, *Government Shuts Down Website for Doctors Searching for Treatment Guidelines*, CNN HEALTH (July 16, 2018), <https://www.cnn.com/2018/07/16/health/hhs-website-shuts-down/index.html>. Although NGC's definition of "clinical practice guidelines" was identical to the IMO's definition, the inclusion criteria were not identical to the trustworthiness criteria. *NGC and NQMC Inclusion Criteria*, AGENCY FOR HEALTHCARE RSCH. & QUALITY, <https://www.ahrq.gov/gam/summaries/inclusion-criteria/index.html#ref2> (last visited Oct. 14, 2020). More importantly, however, funding for the program ran out in 2018. Scutti, *supra*.

¹⁵⁶ As a reference point, we could consider the effort and expense that was required to unearth just the opacity of compendia. See *infra* Part II.

¹⁵⁷ In 2008, the IOM found over 3,700 total CPGs in the Guidelines International Network database, and 722 accepted guidelines by the NGC in that year alone. IOM REPORT, *supra* note 75, at 2.

is either wrong-headed¹⁵⁸ or spot on as a matter of First Amendment doctrine.¹⁵⁹ Other scholarship is predictive, analyzing how recent decisions shape future attempts to regulate off-label promotion¹⁶⁰ or cause knock-on effects in other areas of drug regulation.¹⁶¹ This Article's proposal is none of these things. Rather than predict, criticize, or applaud First Amendment challenges, it satisfies them by creating a nuanced regulatory regime that is sensitive to evidence.

¹⁵⁸ E.g., Christopher Robertson, *When Truth Cannot Be Presumed: The Regulation of Drug Promotion Under an Expanding First Amendment*, 94 B.U. L. REV. 545, 546–55 (2014) (arguing current FDCA regime is constitutionally “precarious” due to viewpoint discrimination); Christopher Robertson, *The Tip of the Iceberg: A First Amendment Right to Promote Drugs Off-Label*, 78 OHIO ST. L.J. 1019, 1025–30 (2017) (showing inconsistency in prosecution of those promoting an unapproved drug and those promoting an approved drug for an unapproved use despite the identical legal theory for prosecution); Stephanie M. Greene, *After Caronia: First Amendment Concerns in Off-Label Promotion*, 51 SAN DIEGO L. REV. 645, 683–704 (2014) (arguing off-label promotion is false and misleading speech); Stephanie M. Greene, Debate Opening Statement, *Off-Label Drug Promotion and the First Amendment*, 162 U. PA. L. REV. ONLINE 239, 247 (2014) (arguing that First Amendment concerns are “easily overcome”); Cynthia M. Ho, *A Dangerous Concoction: Pharmaceutical Marketing, Cognitive Biases, and First Amendment Overprotection*, 94 IND. L.J. 773, 802–26, 831 (2019) (arguing that empirical assumptions underlying First Amendment doctrine in pharmaceutical advertising are false and reflect cognitive biases, and that courts are making legal decisions through unwarranted or unsubstantiated schemas). Some scholarship argues court decisions do not pose an impediment to FDA regulation. See Dina McKenney, *Off-Label Drug Promotion and the Use of Disclaimers*, 92 TEX. L. REV. 231, 245–48 (2013) (arguing for a disclaimer regime for off-label promotion); Constance E. Bagley, Joshua Mitts & Richard J. Tinsley, *Snake Oil Salesman or Purveyors of Knowledge: Off-Label Promotions and the Commercial Speech Doctrine*, 23 CORNELL J. L. & PUB. POL’Y 337, 341 (2013) (advancing standard focused on reducing economic paternalism and scrutinizing discriminatory agency behavior).

¹⁵⁹ E.g., Coleen Klasmeier & Martin H. Redish, *Off-Label Prescription Advertising, the FDA and the First Amendment: A Study in the Values of Commercial Speech Protection*, 37 AM. J. L. & MED. 315, 317, 356 (2011) (arguing the FDA’s attempts to regulate off-label promotion are unconstitutional); Lars Noah, Essay, *Banning Off-Label Drug Promotion Offends the U.S. Constitution: Making the Strongest Case*, 83 ALB. L. REV. 301, 302, 306–08 (2019/2020) (arguing treatment of generic manufacturers under off-label promotion rules is unconstitutional); Lars Noah, Debate Rebuttal, *Off-Label Drug Promotion and the First Amendment*, 162 U. PA. L. REV. ONLINE 239, 251 (2014) (arguing for unconstitutionality of off-label promotion); Lars Noah, *What’s Wrong with “Constitutionalizing Food and Drug Law”?*, 75 TUL. L. REV. 137, 137, 148 (2000) (advocating constitutional resolution to off-label speech regulation despite constitutional avoidance cannon); Carl Wiersum, *No Longer Business as Usual: FDA Exceptionalism, Commercial Speech, and the First Amendment*, 73 FOOD & DRUG L.J. 486, 552–55 (2018) (arguing the FDA has continually been forced to retreat from its regulatory posture over speech and that this approach is unlikely to continue given directions in First Amendment jurisprudence).

¹⁶⁰ E.g., Krista Hessler Carver, *A Global View of the First Amendment Constraints on FDA*, 63 FOOD & DRUG L.J. 151, 209–13 (2008); Margaret Gilhooley, *Commercial Speech, Drugs, Promotion and a Tailored Advertisement Moratorium*, 21 HEALTH MATRIX 97, 108 (2011); see Sam F. Halabi, *Off-Label Marketing’s Audiences: The 21st Century Cures Act and the Relaxation of Standards for Evidence-Based Therapeutic and Cost-Comparative Claims*, 44 AM. J. L. & MED. 181–96 (2018). (describing how the 21st Century Cures Act (2016) removed barriers for certain kinds of off-label promotion).

¹⁶¹ See Patricia J. Zettler, *The Indirect Consequences of Expanded Off-Label Promotion*, 78 OHIO ST. L.J. 1053, 1076–97 (2017) (describing how off-label regulation can cause knock-on effects for other areas of drug regulation).

By narrowly tailoring regulations to the evidence base for each use, this proposal solves the constitutional problem created by *WLF* and *Caronia*. Under this approach, the FDA has a strong argument to defeat the principal failure of its regulations under the last two prongs of *Central Hudson*: (1) “direct advancement” of substantial government interest that is (2) “narrowly drawn.”¹⁶² In *Caronia*, unlike in *WLF*,¹⁶³ the court concluded that the FDA’s guidance documents did not directly advance a substantial government interest for two reasons. First, the FDA did not show how limiting information could decrease patient risk.¹⁶⁴ Second, the FDA Guidance Documents inhibited potentially useful information to physicians while leaving the practice that gave rise to the promotion at issue, off-label prescribing, unregulated.¹⁶⁵ And in both *Caronia* and *WLF I*, the FDA regulations were not narrowly drawn either, because there were “less speech-restrictive alternatives . . . available.”¹⁶⁶ As noted above, the courts’ options included disclaimers¹⁶⁷ and physician education,¹⁶⁸ as well as caps on off-label prescriptions.¹⁶⁹

But under an approach that is finely attuned to evidence, the FDA can more confidently assert that all three of these statements are no longer true. Because the level of information is directly linked to the evidence for the use, information is limited based on patient risk and value to physicians. Safer and more useful information is limited less than unsafe and unreliable information. And the limitations are drawn based on evidence as determined by experts rating it.

Although it is possible to argue that a disclaimer system is still “less speech restrictive,” that is largely a red herring. If that reading is correct, then the *only* way the FDA can regulate off-label promotion is through disclaimers. And that is not what the courts in either *WLF* or *Caronia* said; they said only that less speech restrictive means were available, using the disclaimer system as one example.

¹⁶² *Cent. Hudson Gas & Elec. Corp. v. Pub. Serv. Comm’n*, 447 U.S. 557, 564–65 (1980).

¹⁶³ In *WLF I*, the court found that the FDA’s guidance documents *did* directly advance a substantial government interest of pressuring manufacturers to move new uses on-label. 13 F. Supp. 2d 51, 72 (D.D.C. 1998). But it ultimately held them unconstitutional because they failed the fourth prong of *Central Hudson*. *Id.* at 72–74. The final injunction, later vacated, did limit the FDA’s authority to regulate off-label promotion. *WLF III*, 202 F.3d 331, 334–35 (D.C. Cir. 2000).

¹⁶⁴ *United States v. Caronia*, 703 F.3d 149, 166 (2d Cir. 2012).

¹⁶⁵ *Id.* at 166–67.

¹⁶⁶ *Id.* at 167; *WLF I*, 13 F. Supp. 2d at 73.

¹⁶⁷ *WLF I*, 13 F. Supp. 2d at 73–74 (arguing a “full, complete, and unambiguous disclosure by the manufacturer” would achieve the FDA’s goals in a way that did not offend the First Amendment).

¹⁶⁸ *Caronia*, 703 F.3d at 168.

¹⁶⁹ *Id.*

The approach suggested here is less speech-restrictive than the FDA's current approach. An evidence-based framework is not only "narrowly drawn" but also is a tight fit. Even if truthful off-label promotion is allowed after *Caronia*, the FDA can use this framework as a tool for helping articulate when speech is likely to be misleading—and do so in a way that is likely to withstand legal attack.

This approach also fixes the problems of rigidity and vagueness by detailing grounded trustworthiness criteria. That, in turn, opens the possibility of efficiently specifying different requirements for content, format, manner of distribution—and potentially even for the types of materials that could be distributed (i.e., not just scientific articles, reference texts, and CPGs). Because the FDA would have an evidentiary grade in hand, it could more clearly specify the type and nature of activities permitted for each use with the assigned grade. Importantly, it would also enable the FDA to draft a uniform disclosure document, like the one in the Appendix, that it could require drug companies to include in all off-label communications.

Not only will this approach solve the FDA's legal and practical problems, but it will further the FDA's goal of ensuring firms have incentives to invest in information generation about new uses.¹⁷⁰ The flexible regulations allow a more fine-grained approach that can be specific enough to weed out activities that are allowed for only approved drugs, while being sensitive enough to cabin the permissible activities to lubricate information flow to physicians about new uses.¹⁷¹

II. DRUG COMPENDIA

Regulation of information about off-label uses should reflect the evidence base for the use in question. Regulation should be less restrictive for uses supported by strong evidence and more restrictive for those supported by weak

¹⁷⁰ There is not good evidence about when and why firms file for sNDAs. It is not clear, for example, how much of firm activity is driven by existing patents or data exclusivities. *But see* Babak Sahragardjoonegani, Reed F. Beall, Aaron S. Kesselheim & Aidan Hollis, *Repurposing Existing Drugs for New Uses: A Cohort Study of the Frequency of FDA-Granted New Indication Exclusivities Since 1997*, 14 J. PHARM POL'Y & PRAC. 1, 6 (2021); Simon, *supra* note 5, at 729 n.121.

¹⁷¹ And it also raises a different possibility—the possibility that more permissive information flows would actually *improve* the evidence base for off-label uses. Firms that know that more information will potentially lead to better advertising will tend to try to produce it, though they may try to produce it at the exclusion of other, harmful information. *But see* Daniel R. Cahoy, *Medical Product Information Incentives and the Transparency Paradox*, 82 IND. L.J. 623 (2007) (explaining that tort incentives actually deter firms from generating information about their drugs after FDA approval).

or no evidence. This Part and the one that follows argue that the best way to implement this approach is to rely on existing private sources of information about the evidence base for each use: drug compendia.

The primary purpose of this Part is to explain what drug compendia are, why and how they are used by the CMS, and their limitations. Section A briefly explains the history of drug compendia and their current role in drug reimbursement. It shows how the CMS farms out to compendia the process of evaluating off-label drug therapies for reimbursement. Drugs and uses that appear in “recognized” compendia, by and large, will be reimbursed by Medicare and Medicaid; drugs that make no appearance, by contrast, will not be.¹⁷² Sections B and C then explain that compendia, despite their freedom, are not unregulated. The CMS polices drug compendia in two ways. First, it regulates compendia *directly* by setting requirements with which compendia must comply to be “recognized” for reimbursement purposes. Second, the CMS regulates compendia *indirectly* by specifying the quality of evidence it will accept for reimbursement. Finally, Section D explores the limitations of compendia; namely, that they are inconsistent, opaque, and biased.

A. *Drug Compendia, Generally*

Drug compendia are informational books (now mostly in electronic form) about pharmaceuticals organized and published by private organizations.¹⁷³ Since the first national compendium, the *Pharmacopoeia of the United States of America* (“USP”), was published in 1820, the size, scope, and function of compendia have changed dramatically.¹⁷⁴ When the first edition of the USP hit the shelves, the marketplace for drugs—and the practice of medicine—was markedly different from today. At that time, so-called “patent medicines”—medicines that were not covered by a patent but whose ingredients were instead kept “secret”¹⁷⁵—littered the shelves of pharmacies.

¹⁷² For the implications of this system, see David A. Simon, *The Other FDA 8–13* (Oct. 24, 2022) (unpublished manuscript) (on file with author).

¹⁷³ Katherine Tillman, Brijet Burton, Louis B. Jacques & Steve E. Phurrough, *Compendia and Anticancer Therapy Under Medicare*, 150 *ANNALS INTERNAL MED.* 348, 348 (2009) (“In the pharmaceutical industry, a compendium is a comprehensive listing of drugs and biologicals. It typically includes a summary of the pharmacologic characteristics of each listed drug or biological; information on dosage; and, often, recommended uses for specific diseases. Some insurers refer to compendia when making policy decisions, thus creating a strong financial incentive for manufacturers to obtain a favorable compendium recommendation.”).

¹⁷⁴ JOSEPH M. GABRIEL, *MEDICAL MONOPOLY: INTELLECTUAL PROPERTY RIGHTS AND THE ORIGINS OF THE MODERN PHARMACEUTICAL INDUSTRY* 36–37 (2014).

¹⁷⁵ *Id.* at 9 (noting that the term “patent medicines” was used “because [the medicines] were supposedly protected by patents granted by the king of England”).

Within this environment, reformers saw a clear need to establish a common language and normative framework that assisted in therapeutic decision-making.¹⁷⁶ The former was important because of both the varieties of substance names and the sheer number of patent medicines. The latter was critical to ensure accurate dispensing and treatment. Both of these goals were central to a third: making the compendium practically useful to physicians.¹⁷⁷

Over time, the USP became an important tool for food and drug regulation. Many state laws, for example, prohibited “adulterated drugs,” which were defined by reference to the “standards and formula set out in the USP.”¹⁷⁸ It obtained “quasi-official status” under the Drug Importation Act of 1848, which enabled import officers to refuse entry based on standards in the USP.¹⁷⁹ By 1908, the USP, along with the National Formulary (“NF”),¹⁸⁰ had become so important that Congress explicitly recognized them as the “‘official compendia’ and as legal standards for identity, strength, quality, and purity of drugs.”¹⁸¹

Economic and cultural differences that emerged over the next 150 years also made the USP strikingly different than the compendia used today. The original USP, for example, excluded all medicines protected by patent because, until at least 1882, the medical community viewed patented medicines as illegitimate.¹⁸² This is, of course, no longer true. Compendia currently contain patented and unpatented medicines alike. And they also contain far more information—in quantity, kind, and complexity—than the early versions of the USP.

¹⁷⁶ *Id.* at 36–37; see also Martin I. Blake, *The Role of the Compendia in Establishing Drug Standards*, 31 FOOD DRUG COSM. L.J. 276, 277 (1976) (noting that the purpose of the USP was “to establish formulas or recipes for the preparation of dosage forms”).

¹⁷⁷ GABRIEL, *supra* note 174, at 37–41.

¹⁷⁸ *Id.* at 109 (emphasis omitted).

¹⁷⁹ Import Drug Act of 1848, ch. 70, § 3, 9 Stat. 237, 238 (1848); JAMES HARVEY YOUNG, PURE FOOD: SECURING THE FEDERAL FOOD AND DRUGS ACT OF 1906, at 14 (1989). The USP was one of five pharmacopoeias used by import officers. YOUNG, *supra* (“[T]he examiner was empowered to reject drugs adulterated or deteriorated below the standards set in the United States, Edinburgh, London, French and German pharmacopoeias and dispensaries . . .” (internal quotation marks omitted)).

¹⁸⁰ The NF supplements the USP. George Urdang & Glenn Sonnedecker, *Authoritative English-Language Drug Compendia Supplementing Pharmacopoeias*, 8 FOOD DRUG COSM. L.J. 485, 488 (1953).

¹⁸¹ Blake, *supra* note 176, at 278 (emphasis omitted); Pure Food and Drug Act of 1906, Pub. L. No. 59-384, §§ 6, 7, 34 Stat. 768, 769–70 (defining “drug” and “adulterated” by references to standards in the USP and NF); Food, Drug, and Cosmetic Act, 21 U.S.C. § 321(j) (amended 2022) (defining “official compendium” to be the USP, the NF, and the Homeopathic Pharmacopoeia); Food, Drug, and Cosmetic Act, 21 U.S.C. §§ 351, 352 (amended 2022) (describing adulterated and misbranded drugs by reference to standards and names set in the official compendium).

¹⁸² GABRIEL, *supra* note 174, at 109. This led to debates about whether patented medicines should be included in the USP as they proliferated. *Id.* at 143–44, 169–70.

Although current compendia's role in the practice of medicine is, in some ways, substantially different than the original USP, they are no less important. Within the U.S. healthcare system, compendia occupy two crucial and intimately related roles.¹⁸³ The first is standard setting. Just as it did over a century ago, federal law relies on the USP, along with other compendia, to set various standards, including those for drug purity.¹⁸⁴

The second is drug coverage and reimbursement for public insurance. Medicare and Medicaid are public insurance programs that cover almost half of all Americans;¹⁸⁵ the former insures low-income individuals and the latter insures seniors and the disabled. Medicare Part A covers drugs administered during a stay in a hospital or a skilled nursing facility.¹⁸⁶ Medicare Part B covers a limited number of drugs administered by a physician in an outpatient setting.¹⁸⁷ Since Medicare expanded to cover prescription drugs in 2003, the CMS has set

¹⁸³ Compendia are defined at 42 C.F.R. § 414.930(a) (2021).

¹⁸⁴ *E.g.*, 21 U.S.C. § 353a(b)(1)(A)(i)(I) (requiring “bulk drug substances” to “comply with the standards of an applicable United States Pharmacopoeia or National Formulary monograph, if a monograph exists, and the United States Pharmacopoeia chapter on pharmacy compounding”); *id.* § 353b(a)(2)(B) (prohibiting “bulk drug substances” unless, among other exceptions, the substance complies with an applicable monograph that exists in the USP or other recognized compendia); *id.* § 351(b) (defining adulterated drugs as those that differ in “strength, quality, or purity” from the drugs as described in official compendia). A related use is to define “therapeutic classes.” 42 U.S.C. § 1395w-104(b)(3)(C)(ii) (requiring the HHS to request the USP develop a model formulary for prescription drugs); 21 U.S.C. § 355(u)(3) (defining “therapeutic category” for certain new drug applications).

¹⁸⁵ *See* MEDICARE PAYMENT ADVISORY COMM'N, REPORT TO THE CONGRESS: MEDICARE PAYMENT 405 (2020) (explaining Medicare covers 45.4 million beneficiaries under Part D). Medicaid and Children's Health Insurance Programs (“CHIP”) beneficiaries total more than 88.9 million. *See May 2022 Medicaid & CHIP Enrollment Data Highlights*, MEDICAID.GOV, <https://www.medicaid.gov/medicaid/program-information/medicaid-and-chip-enrollment-data/report-highlights/index.html> (last visited Sept. 26, 2022) (includes those enrolled in CHIP).

¹⁸⁶ 42 U.S.C. § 1395d(a) (describing inpatient coverage); *id.* § 1395x(b)(2)–(3) (covering inpatient “drugs” and “biologicals” and “such other diagnostic or therapeutic items or services, furnished by the hospital”); *id.* § 1395x(h) (covering “drugs” and “biologicals” delivered as part of an extended stay in a skilled nursing facility).

¹⁸⁷ *Id.* § 1395k (defining Part B coverage to include payment for “for medical and other health services”); *id.* § 1395x(s) (defining “medical and other health services”); *id.* § 1395x(s)(2)(A) (“furnished as an incident to a physician's professional service”); *id.* § 1395x(s)(2)(J) (“prescription drugs used in immunosuppressive therapy furnished, to an individual who receives an organ transplant for which payment is made under this subchapter”); *id.* § 1395x(s)(2)(I) (blood clotting factors); *id.* § 1395x(s)(2)(O) (“erythropoietin for dialysis patients competent to use such drug without medical or other supervision”); *id.* § 1395x(s)(2)(Q) (oral anticancer drugs by prescription that would be covered if administered by a physician or in a hospital); *id.* § 1395u(o) (setting reimbursement rates of drugs and biologics “[i]f a physician's, supplier's, or any other person's bill or request for payment for services includes a charge for a drug or biological for which payment may be made under this part and the drug or biological is not paid on a cost or prospective payment basis as otherwise provided in this part”).

drug coverage and reimbursement criteria for its beneficiaries and has exercised considerable weight in setting the same criteria for private industry.¹⁸⁸

Medicare Parts A and B will cover drugs only when they are “reasonable and necessary for the diagnosis or treatment of illness or injury”¹⁸⁹—though this term is not defined by statute or regulations.¹⁹⁰ In 1993, however, Congress explicitly defined a covered drug to include a use in an “anticancer chemotherapeutic regimen” for a “medically accepted indication,” which it defined as being included in and supported by certain compendia.¹⁹¹ Currently, all other off-label uses can be reimbursed at the discretion of the local contractor administering Parts A/B when it “determines the use to be medically accepted, taking into consideration the major drug compendia, authoritative medical literature and/or accepted standards of medical practice.”¹⁹²

When Congress enacted Medicare Part D in 2003, it expressly defined covered drugs as those used for “medically accepted indications,”¹⁹³ though it

¹⁸⁸ ROSS MCKINNEY, AMY P. ABERNETHY, DAVID B. MATCHAR & JANE L. WHEELER, AHRQ TECH. ASSESSMENT PROGRAM, WHITE PAPER: POTENTIAL CONFLICT OF INTEREST IN THE PRODUCTION OF DRUG COMPENDIA 5 (2009) [hereinafter AHRQ 2009 WHITE PAPER], <https://www.cms.gov/Medicare/Coverage/DeterminationProcess/downloads/id64ta.pdf>.

¹⁸⁹ 42 U.S.C. § 1395y(a)(1)(A) (emphasis added).

¹⁹⁰ Rachel E. Sachs, *Delinking Reimbursement*, 102 MINN. L. REV. 2307, 2314–15 (2018) (first citing Isaac D. Buck, *Furthering the Fiduciary Metaphor: The Duty of Providers to the Payers of Medicare*, 104 CALIF. L. REV. 1043, 1068–69 (2016); and then citing Peter J. Neumann & James D. Chambers, *Medicare’s Enduring Struggle to Define “Reasonable and Necessary” Care*, 367 NEW ENG. J. MED. 1775, 1775–76 (2012)). Recently, however, the CMS did define “reasonable and necessary,” but repealed the rule shortly thereafter. Medicare Program; Medicare Coverage of Innovative Technology (MCIT) and Definition of “Reasonable and Necessary,” 86 Fed. Reg. 62944 (Nov. 15, 2021) (to be codified at 42 C.F.R. pt. 405).

¹⁹¹ Omnibus Budget Reconciliation Act of 1993, Pub. L. No. 103-66, § 13553(b), 107 Stat. 312, 591–92 (codified at 42 U.S.C. § 1395x(t)(2)(B)) (listing original compendia as “the American Hospital Formulary Service-Drug Information, the American Medical Association Drug Evaluations, the United States Pharmacopoeia-Drug Information, and other authoritative compendia as identified by the Secretary”). Part B covered oral cancer drugs on an outpatient basis provided those drugs would be covered if they had been administered by a physician or during an inpatient hospital stay. 42 U.S.C. § 1395x(s)(2)(Q). The compendia system was also used for Medicaid, which defines “medically accepted indication” as an approved use or one covered by three compendia listed in the statute (though only two of the three remain active). Social Security Act § 1927(g)(1)(B)(i)(I)–(III), 42 U.S.C. § 1396r-8(g)(1)(B)(i)(I)–(III).

¹⁹² MEDICARE BENEFIT POLICY MANUAL, CHAPTER 15—COVERED MEDICAL AND OTHER HEALTH SERVICES §§ 50.4.2, 50.4.5 (2022), <https://www.cms.gov/Regulations-and-Guidance/Guidance/Manuals/Downloads/bp102c15.pdf> (“FDA-approved drugs and biologicals may also be considered for use in the determination of medically accepted indications for off-label use if determined by the contractor to be reasonable and necessary.”).

¹⁹³ 42 U.S.C. § 1395w-102(e)(1) (defining a “covered part D drug” to mean a drug sold on prescription and “any use of a covered part D drug for a medically accepted indication”); *id.* § 1395w-102(e)(4) (defining “medically accepted indication” of a “covered Part D” for cancer to include drugs the compendia “described in clause (ii)(I) section 1395x(t)(2)(B)” of the Social Security Act and for all other drugs as the term is defined by 42 U.S.C. 1396r-8(k)(6), which, in turn, means any approved drug for which the use is supported by one or more

did not include a list of compendia.¹⁹⁴ In 2008, it expanded Part D coverage for anticancer drugs to be consistent with Part B coverage of anticancer drugs by including additional compendia that could support such a determination that the drug was used for a medically accepted indication.¹⁹⁵ A similar rule applies to *all non-cancer off-label* uses under Medicare Part D, though the list of compendia is limited to the two existing statutory compendia listed as defining “medically-accepted indications” under the outpatient coverage portion of Medicaid.¹⁹⁶ Subject to certain evidentiary requirements, discussed below in Section C, Medicare will cover and reimburse for uses, even off-label uses, listed in compendia unless at least one compendium rates the use as poorly supported.¹⁹⁷

citations included or approved for inclusion in any of the compendia described in the Social Security Act § 1927(g)(1)(B)(i), 42 U.S.C. § 1396r-8(g)(1)(B)(i). This is also true for outpatient drug coverage under Medicaid, though the list of compendia is different. *Id.* § 1396r-8(k)(6) (defining “medically accepted indication” for purposes of outpatient drug coverage under Medicaid).

The same section that defines “covered part D drug” also specifically allows Medicare Advantage Prescription Drug Plan to exclude from coverage any drug that would not be covered if “payment would not be made if section 1395y(a) of this title applied to this part.” *Id.* § 1395w-102(e)(3)(A). Section 1395y(a), of course, is the section of the Social Security Act requiring items and services to be “reasonable and necessary” for treatment. *Id.* § 1395y(a); *see also* MEDICARE BENEFIT POLICY MANUAL, *supra* note 192, § 50.4.5 (“FDA-approved drugs and biologicals may also be considered for use in the determination of medically accepted indications for off-label use if determined by the contractor to be reasonable and necessary.”).

¹⁹⁴ Medicare Prescription Drug, Improvement, and Modernization Act of 2003, Pub. L. No. 108-173, § 1860D-2, 117 Stat. 2066, 2080–81 (codified at 42 U.S.C. 1395w-102(e)).

¹⁹⁵ Medicare Improvements for Patients and Providers Act of 2008, Pub. L. No. 110-275, § 182, 122 Stat. 2494, 2583 (codified at Social Security Act § 1860D-2(e)(1), 42 U.S.C. § 1395w-102(e)(1)). This statute expanded the compendia Medicare would consider under Part D when covering oral cancer drugs from the original three used by Part B—the American Hospital Formulary Service-Drug Information, the American Medical Association Drug Evaluations, and the United States Pharmacopoeia-Drug Information, 42 U.S.C. § 1395x(t)(2)(B)—to five, adding two that Medicaid used for coverage: “(II) United States Pharmacopoeia-Drug Information (or its successor publications)[,] and (III) the DRUGDEX Information System.” 42 U.S.C. § 1396r-8(g)(1)(B)(i); *id.* § 1395w-102(e)(4) (defining “medically accepted indication” of a covered Part D drug to include the compendia referenced in § 1396r-8(g)(1)(B)(i), which are the ones named in the preceding sentence); *see also* MEDICARE PRESCRIPTION DRUG BENEFIT MANUAL, CHAPTER 6—PART D DRUGS AND FORMULARY REQUIREMENTS § 10.6 (2016), <https://www.cms.gov/medicare/prescription-drug-coverage/prescriptiondrugcovcontra/downloads/part-d-benefits-manual-chapter-6.pdf>.

¹⁹⁶ MEDICARE PRESCRIPTION DRUG BENEFIT MANUAL, *supra* note 195 (noting there are only two recognized compendia for all Part D drugs: American Hospital Formulary Service Drug Information and DRUGDEX® Information System). Importantly, however, Part D plans are subject to a different range of reimbursement rules, with discretion of plans to implement formulary requirements and step-therapy requirements. *Id.* (noting Part D sponsors can use utilization techniques to make these determinations, i.e., determinations that applies to drug classes rather than specific uses). Oral cancer drugs, on the other hand, are usually paid for by Medicare Part B, which requires diagnosis codes on prescriptions. Simon, *supra* note 172, at 25. Because many Part D drugs do not require diagnosis codes, whether the prescribed use is included in the specified compendia may be irrelevant—without this information, the drug will simply be reimbursed as if it was prescribed on-label unless it is subject to utilization management.

¹⁹⁷ The exception applies when “the Secretary has determined that the use is not medically appropriate or the use is identified as not indicated in one or more such compendia.” 42 U.S.C. § 1395x(t)(ii)(I). Medicare’s

Because Medicare is the single largest insurer in the United States, its decision to reimburse drugs listed in compendia has significant influence on private providers.¹⁹⁸ This influence can affect treatment decisions in some practice areas.¹⁹⁹ Providers can consult compendia to see whether a drug is covered for a particular use. For practice areas like oncology, where on-label treatments are scarce and the cost of drugs is high, this information is important.²⁰⁰ But even in other practice areas coverage can influence prescribing behavior. In this way compendia influence both coverage and treatment.

B. Direct Regulation of Compendia

Until very recently, this influence was not regulated directly. The 1993 legislation merely recognized compendia for cancer drugs and stated that the Secretary of Health and Human Services (“HHS”) could amend the enumerated list.²⁰¹ It made no attempt to mandate that compendia conform to any quality

payment manual explains that the meaning of “not indicated” can vary by compendia and explains how to determine if a drug is “medically accepted” by reference to the relevant ratings in each compendium. MEDICARE BENEFIT POLICY MANUAL, *supra* note 192, § 50.4.5. Being “medically accepted” means that no compendia list the drug as “not indicated.” *Id.*

¹⁹⁸ See Joshua Cohen, Andrew Wilson & Laura Faden, *Off-Label Use Reimbursement*, 64 FOOD & DRUG L.J. 391, 397–98 (2009). Private providers administer Medicare Part D programs. Some compendia also have significant international influence. *E.g.*, Robert W. Carlson, Jonathan K. Larsen, Joan McClure, C. Lyn Fitzgerald, Alan P. Venook, Al B. Benson III & Benjamin O. Anderson, *International Adaptations of NCCN Clinical Practice Guidelines in Oncology*, 12 J. NAT’L COMPREHENSIVE CANCER NETWORK 643–48 (2014). And many states have laws that require coverage of off-label cancer drugs if they appear in compendia. *E.g.*, N.Y. INS. LAW § 3221 (McKinney 2022); MD. CODE ANN., INS. § 15-804 (West 2009); Am. Soc. of Clinical Oncology, *Reimbursement for Cancer Treatment: Coverage of Off-Label Drug Indications*, 24 J. CLINICAL ONCOLOGY 3206, 3207 (2006).

¹⁹⁹ AHRQ 2009 WHITE PAPER, *supra* note 188, at 5 (noting that because most third-party payors and states follow CMS’s use of the compendia for reimbursement decisions, “[t]he four approved compendia thus heavily influence, if not determine, treatment decisions for many cancer patients”); see Cohen, Wilson & Faden, *supra* note 198, at 391 & n.1, 398 (“updating” the study by Raiford, Shulman & Lasagna, *infra*, explaining variation in payor reimbursement decisions for off-label use and finding that “[n]early 90 percent of respondents said that compendia play a role in decisions to reimburse specific off-label indications, while only nine percent said that compendia played no role”); Drusilla S. Raiford, Sheila R. Shulman & Louis Lasagna, *Determining Appropriate Reimbursement for Prescription Drugs: Off Label Uses and Investigational Therapies*, 49 FOOD & DRUG L.J. 37, 49–50 (1994) (explaining survey results of private payors showed that 67% of respondents indicated that they used compendia “in some way” to make reimbursement decisions). The difference between 2009 and 1994 was, no doubt, partially a result of the increasingly important role compendia played in Medicare and Medicaid reimbursement.

²⁰⁰ Though it is not clear how much practitioners use this information. See MARCH 30, 2006 MCAC VOTES ON QUESTIONS AS AMENDED BY THE MCAC (2006) [hereinafter MEDCAC REPORT], <https://www.cms.gov/Regulations-and-Guidance/Guidance/FACA/downloads/id33c.pdf> (question 9). Some research suggests that providers rely more on what Peter Temin has called a customary/market model. TEMIN, *supra* note 37, at 88–90, 106–19.

²⁰¹ Omnibus Budget Reconciliation Act of 1993, Pub. L. No. 103-66, § 13553(b), 107 Stat. 312, 591–92 (codified at 42 U.S.C. § 1395x(t)(2)(B)).

standards. Regulatory change, however, did come—twice. The first adjustment occurred in a 2007,²⁰² shortly after the Medicare Coverage Advisory Committee’s (“MEDCAC”)²⁰³ 2006 study of compendia reliability.²⁰⁴ As a result of this study and a subsequent MEDCAC meeting,²⁰⁵ the CMS identified desirable characteristics of compendia (“MEDCAC Characteristics”), which it folded into new admission criteria for compendia that sought recognized status under the 1993 law.²⁰⁶

These included the “breadth of listings,” processing times for inclusion, a “detailed description” of evidence in each entry, “criteria for weighing evidence,” a “published process for making recommendations,” a “[p]ublicly transparent process for evaluating therapies,” explicit listing of a therapy as “[n]ot recommended” when evidence indicates, and a public process for identifying, notifying, and managing potential and recognized conflicts of interests.²⁰⁷ Although the CMS did not rank these characteristics by importance, it highlighted transparency and conflict of interest as being “high priority to preserve the integrity [of,] and minimize bias during[,] the review process.”²⁰⁸ The CMS also stated that it would consider “a compendium’s grading of

²⁰² See Medicare Program Revisions, 72 Fed. Reg. 66222, 66304 (Nov. 27, 2007).

²⁰³ The CMS established MEDCAC under a two-year charter in 1998. Establishment of the Medicare Coverage Advisory Committee and Request for Nominations for Members, 63 Fed. Reg. 68780, 68780 (Dec. 14, 1998). It was designed “to provide independent guidance and expert advice to CMS on specific clinical topics.” *Factors CMS Considers in Referring Topics to the Medicare Evidence Development & Coverage Advisory Committee Document Issued*, CMS.GOV (Dec. 12, 2006), <https://www.cms.gov/medicare-coverage-database/view/medicare-coverage-document.aspx?MCDId=10>.

²⁰⁴ AHRQ 2009 WHITE PAPER, *supra* note 188, at 4–5; AMY P. ABERNETHY, JULIE M. HAMMOND, MICHAEL L. HUBBARD, MEENAL B. PATWARDHAN, LORI A. ORLANDO, DOUGLAS C. MCCRORY, ETHAN BALK, GOWRI RAMAN, PRISCILLA CHEW, BRUCE KUPELNICK ET AL., AHRQ TECH. ASSESSMENT PROGRAM, COMPENDIA FOR COVERAGE OF OFF-LABEL USES OF DRUGS AND BIOLOGICS IN AN ANTICANCER CHEMOTHERAPEUTIC REGIMEN 1 (2007) [hereinafter AHRQ 2007 COMPENDIA COVERAGE], <https://www.hhs.gov/guidance/sites/default/files/hhs-guidance-documents/id46TA.pdf>; *Compendia for Coverage of Off-Label Uses of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen*, CMS.GOV (Mar. 30, 2006) [hereinafter MEDCAC Meeting], <https://www.cms.gov/medicare-coverage-database/view/medcac-meeting.aspx?MEDCACId=33&TAId=46&fromdb=true&bc=AAAAAAAAACAAA&> (last visited July 13, 2020). Previous studies also found inconsistencies. *E.g.*, Cohen, Wilson & Faden, *supra* note 198, at 396–97.

²⁰⁵ MEDCAC Meeting, *supra* note 204.

²⁰⁶ Medicare Program Revisions, 72 Fed. Reg. 66222, 66303–06 (Nov. 27, 2007) (codified at 42 C.F.R. § 414.930(b)(iii)–(iv)). This process, which also included details about how to apply for recognized status, was codified at 42 C.F.R. § 414.930(a)–(c), which was effective from January 1, 2008 to December 31, 2009. It was superseded by the current regulations with the same citation but different substantive provisions. *Compendia for Determination of Medically-Accepted Indications for Off-Label Uses of Drugs and Biologicals*, 74 Fed. Reg. 61901, 61901–04 (Nov. 25, 2009).

²⁰⁷ Medicare Program Revisions, 72 Fed. Reg. 66222, 66304 (Nov. 27, 2007); 42 C.F.R. § 414.930(b)(iii) (2021).

²⁰⁸ Medicare Program Revisions, 72 Fed. Reg. at 66305.

evidence used in making recommendations regarding off-label uses and the process by which the compendium grades the evidence.”²⁰⁹ Finally, it bestowed upon itself the power and discretion to consider “additional reasonable factors.”²¹⁰ Although these new admission criteria were an important regulatory advance, none of them was per se compulsory; they were merely “guidance and a framework” for how the CMS would evaluate requests to add new compendia.²¹¹ In practice, however, the CMS has treated them as mandatory.²¹²

Several requests for addition rolled in soon after the 2007 public notice. All told, four compendia sought addition in 2008;²¹³ three were ultimately successful, bringing the total number of recognized compendia for cancer drugs to four.²¹⁴ And the criteria CMS identified in its official notice influenced requestor behavior. In every requestor letter, compendia took pains to explain how they met all of the MEDCAC Characteristics.²¹⁵ The CMS, too, explained

²⁰⁹ 42 C.F.R. § 414.930(b)(iv).

²¹⁰ Medicare Program Revisions, 72 Fed. Reg. at 66306 (“For example, we may consider factors that are likely to impact the compendium’s suitability for this use, such as but not restricted to a change in ownership or affiliation, suspension of publication, the standards applicable to the evidence considered by the compendium, and any relevant conflicts of interest. We may consider that broad accessibility by the general public to the information contained in the compendium may assist beneficiaries, their treating physicians, or both, in choosing among treatment options.”).

²¹¹ Medicare Program Revisions, 72 Fed. Reg. at 66305.

²¹² E.g., *AMA-DE Compendium Revision Request—CAG-00388*, CMS.GOV [hereinafter *AMA-DE Revision Request*] <https://www.cms.gov/medicare-coverage-database/view/medicare-coverage-document.aspx?MCDId=13> (last visited Oct. 21, 2022).

²¹³ Request from William T. McGivney, Chief Exec. Officer, Nat’l Comprehensive Cancer Network, to Ctrs. for Medicare & Medicaid Servs. (Feb. 6, 2008) [hereinafter *NCCN Revision Request*], <https://www.cms.gov/Medicare/Coverage/CoverageGenInfo/downloads/covdoc14.pdf>; Request from Joseph S. Bailes, Gov’t Rels. Council Chair, Am. Soc’y of Clinical Oncology, to Steve Phurrough, Ctrs. for Medicare & Medicaid Servs. (Feb. 11, 2008) [hereinafter *DrugPoints Revision Request*], <https://www.cms.gov/Medicare/Coverage/CoverageGenInfo/downloads/covdoc15.pdf>; Request from Richard Klasco, Senior Vice President for Med. Affs. & Editor-in-Chief, Thomson Healthcare, to Ctrs. for Medicare & Medicaid Servs. (Feb. 13, 2008) [hereinafter *DrugDex Revision Request*], <https://www.cms.gov/Medicare/Coverage/CoverageGenInfo/downloads/covdoc16.pdf>; Request from MaryAnne Hochadel, Vice President, Editor-in-Chief, Gold Standard Inc./ELSEVIER, & Kathleen J. Vieson, Vice President, Dir. of Clinical References, Gold Standard Inc./ELSEVIER, to Ctrs. for Medicare & Medicaid Servs. (Feb. 11, 2008) [hereinafter *Clinical Pharmacology Revision Request*], <https://www.cms.gov/Medicare/Coverage/CoverageGenInfo/downloads/covdoc17.pdf>.CMS.gov.

²¹⁴ The only unsuccessful application was for DrugPoints, which was essentially a pared-down, summary version of Thomson Micromedex and was published by Thomson Healthcare. *Thomson Micromedex DrugPoints Compendium Revision Request—CAG-00390*, CMS.GOV, <https://www.cms.gov/medicare-coverage-database/view/medicare-coverage-document.aspx?MCDId=15> (last visited Oct. 5, 2022); DrugPoints Revision Request, *supra* note 213. American Hospital Formulary Service-Drug Information (“AHFS-DI”) was the only remaining statutorily specified compendium left. It is still recognized by the CMS. MEDICARE PRESCRIPTION DRUG BENEFIT MANUAL, *supra* note 195.

²¹⁵ See *NCCN Revision Request*, *supra* note 213, at 3–5; *DrugPoints Revision Request*, *supra* note 213; *DrugDex Revision Request*, *supra* note 213, at 3–6; *Clinical Pharmacology Revision Request*, *supra* note 213.

its decision to accept or reject a request for addition by reference to whether compendia met these criteria.²¹⁶

This shows that CMS's regulation can affect compendia behavior. The CMS's action also was important for another reason: the CMS itself initiated a request to *remove* American Medical Association Drug Evaluations Compendium, which no longer existed.²¹⁷ This demonstrated that the HHS could both add and remove compendia from the recognized list at its discretion.

Compendia's requests for addition came at just the right time—for them, anyway. In 2008, Congress mandated that “the [recognized] compendia has [sic] a publicly transparent process for evaluating therapies and for identifying potential conflicts of interest[.]”²¹⁸ That command spurred the second change, which occurred in 2009.²¹⁹ Here the impetus was not just a committee report but Congressional action. But before the CMS could explain what kind of process this might be, it had to evaluate the current practices of compendia. And it did. Based on its findings, which were somewhat troubling,²²⁰ it added new admission criteria (“2009 Admission Requirements”).²²¹

Predictably, the new regulatory recipe called for transparency—but it was a rather weak brew. The regulations instituted a Freedom-of-Information-Act-style requirement on compendia to make all information relating to a particular therapy and evaluation—and any identified conflicts of interest—open to the

²¹⁶ *NCCN Compendium Revision Request—CAG-00389*, CMS.GOV [hereinafter *NCCN Decision Letter*], <https://www.cms.gov/medicare-coverage-database/view/medicare-coverage-document.aspx?MCDId=14> (last visited Oct. 21, 2022); *Thomson Micromedex DrugDex ® Compendium Revision Request—CAG-00391*, CMS.GOV [hereinafter *DrugDex Decision Letter*], <https://www.cms.gov/medicare-coverage-database/view/medicare-coverage-document.aspx?MCDId=16> (last visited Oct. 21, 2022); *Clinical Pharmacology Compendium Revision Request—CAG-00392*, CMS.GOV [hereinafter *Clinical Pharmacology Decision Letter*], <https://www.cms.gov/medicare-coverage-database/view/medicare-coverage-document.aspx?MCDId=17> (last visited Oct. 21, 2022); *Wolters Kluwer Clinical Drug Information Lexi-Drugs Compendium Revision Request—CAG-004430*, CMS.GOV [hereinafter *WK Decision Letter*], <https://www.cms.gov/medicare-coverage-database/view/medicare-coverage-document.aspx?MCDId=31> (last visited Oct. 21, 2022).

²¹⁷ *AMA-DE Revision Request*, *supra* note 212.

²¹⁸ Medicare Improvements for Patients and Providers Act of 2008, Pub. L. No. 110-275, § 182, 122 Stat. 2494, 2583; 42 U.S.C. § 1395w-102(e)(4). This same provision, discussed above, also folded Part B and Medicaid compendia into the recognized list of compendia for oral cancer drugs covered under Part D.

²¹⁹ Compendia for Determination of Medically-Accepted Indications for Off-Label Uses of Drugs and Biologicals, 74 Fed. Reg. 61901, 61901–04 (Nov. 25, 2009).

²²⁰ See MEDCAC REPORT, *supra* note 200.

²²¹ Compendia for Determination of Medically-Accepted Indications for Off-Label Uses of Drugs and Biologicals, 74 Fed. Reg. 61901, 61901–04 (Nov. 25, 2009).

public, but only upon a specific request.²²² The requests themselves are not made publicly available.²²³ The public, of course, would have a difficult time even *knowing* what drugs appeared in compendia without a subscription.²²⁴ And requesting this information for *all* drugs and indications listed in the compendia seems beyond the scope of the legislation. This suggests that to obtain the information mandated by the regulations, one must make individual requests of each *indication* listed in the compendia—hardly a simple task.

The move was nevertheless important because it showed yet another (public) method for controlling compendia, or at least holding them accountable. Because of changes to the law in 2008, this same process and standard (as well as any subsequent changes) apply to all recognized compendia under Part D for non-cancer treatment—and to all other off-label uses.²²⁵ To date, no compendia have sought addition to the list of recognized Part D compendia for non-cancer drugs, and neither has CMS—at least not yet.

An opportunity to test these 2009 Admission Requirements as to cancer drugs, however, arose in 2015. That is when Wolters Kluwer requested its Lexi-Drugs database be added to the list of recognized compendia.²²⁶ In its decision approving the request, the CMS noticeably left out any discussion of its 2009 Admission Requirements.²²⁷ It instead relied on the same template it had used

²²² 42 C.F.R. § 414.930(a)(i)–(iii), (i)–(iv), (i)–(ii) (2021) (this provision has three numerical lists, all appearing under Section (a)).

²²³ Most compendia refused to answer any questions about almost any topic. On this score, NCCN specifically refused to provide any further information. Email from Marian Birkeland, Senior Dir., Compendia Dev., Nat'l Comprehensive Cancer Network, to author (Nov. 18, 2020, 10:35 AM) (on file with author).

²²⁴ When it applied, NCCN claimed its compendium was “available free of charge; registration required.” NCCN Revision Request, *supra* note 213, at 1. That no longer appears to be the case. *NCCN Drugs & Biologics Compendium*, NAT'L COMPREHENSIVE CANCER NETWORK, <https://www.nccn.org/Store/Products/description.aspx?productid=9> (last visited Oct. 14, 2020). Lexi-Drugs is available for “trial” for a limited time via smartphone application only. Telephone Interview with Leigh Brag, Sales Representative, Lexi-Drugs (Nov. 16, 2020).

²²⁵ Social Security Act § 1860D-2(e)(4)(A)(C), 42 U.S.C. § 1395w-102(e)(4)(A)(C) (requiring Secretary to revise list of compendia “in section 1927(g)(1)(B)(i) as is appropriate for identifying medically accepted indications for drugs . . . in a manner consistent with the process for revising compendia under section 1861(t)(2)(B)”).

²²⁶ Request from Liz Tomsik, Senior Dir. of Content, Wolters Kluwer, to Ctrs. for Medicare & Medicaid Servs. (Feb. 2, 2015) [hereinafter Lexi-Drugs Revision Request], <https://www.cms.gov/Medicare/Coverage/CoverageGenInfo/Downloads/covdoc31.pdf> (Lexi-Drugs is a database within a larger suite of products offered by Wolters Kluwer).

²²⁷ This increased to five the total number of recognized compendia for cancer drugs. *Wolters Kluwer Clinical Drug Information Lexi-Drugs Compendium Revision Request—CAG-004430*, CMS.GOV, <https://www.cms.gov/medicare-coverage-database/view/medicare-coverage-document.aspx?MCDId=31> (last visited Oct. 21, 2022).

in all of its 2008 decisions.²²⁸ It is not clear whether this decision was purposeful. The CMS could have concluded that Wolters Kluwer's request met the 2009 Admission Requirements based on its published conflicts of interest policy. But that would seem to require the CMS to at least reference the 2009 Admission Requirements, which it did exactly nowhere in its decision.

What this Article has called the MEDCAC Characteristics and 2009 Admission Requirements are a form of direct regulation.²²⁹ While the primary goal of this regulation relates to reimbursement, it has had a rather crucial and somewhat unnoticed effect: to transform the CMS into a mini-FDA for certain off-label uses.²³⁰ Coverage determinations, of course, are made to reduce costs. But *that* objective depends on evaluating the evidence for uses of drugs. Coverage and cost are related to the safety and evidence of a use. An effective therapy is one that works and is therefore worth paying for. An ineffective or unsafe therapy is not. For this reason, the CMS would like to avoid paying for drugs that do not work or are not safe.²³¹

C. Indirect Regulation and Evidence for Uses in Drug Compendia

Simple "inclusion" in a recognized compendium, however, does not guarantee reimbursement by the CMS. That is because not all uses included in compendia are equally supported by evidence. And since the CMS's direct regulation both mandates that compendia rate the evidence for each included use and allows for discretion in how compendia do so, each compendium uses a different system to rate the evidence base for each included off-label use. This, in turn, requires the CMS to regulate compendia *indirectly* by specifying for each compendium the relevant level of evidence needed for a use to merit reimbursement.²³²

Indirect regulation is important precisely because compendia vary widely in how they rate the evidence base for off-label uses. Lexi-Drugs, the newest of the

²²⁸ Compare *WK Decision Letter*, *supra* note 216, with *NCCN Decision Letter*, *supra* note 216, and *DrugDex Decision Letter*, *supra* note 216, and *Clinical Pharmacology Decision Letter*, *supra* note 216.

²²⁹ 42 C.F.R. § 414.930(a) (2021); Medicare Program Revisions, 72 Fed. Reg. 66222, 66303–06 (Nov. 27, 2007). This rule does not apply to non-cancer Part D prescriptions, which are reimbursed using the compendia in the Social Security Act, § 1927(g)(1)(B)(i).

²³⁰ For more on this topic, see Simon, *supra* note 172, at 13–14.

²³¹ The overlap here between safety/efficacy and willingness to pay is not totally exact. The CMS is willing to *pay* for drugs that *may* be effective or are *relatively* safe given the medical need. But willingness to pay based on medical need is not how the FDA evaluates drug approval. So, the CMS may be willing to pay for many uses the FDA would never approve. But the point here is that the CMS is, in effect, taking on the role of the FDA through reimbursement. See Simon, *supra* note 172, at 5.

²³² See *infra* Section III.A.

five recognized compendia, issues recommendations for off-label uses based on an evidentiary rating system.²³³ Evidence falls into four categories: A, B, C, or G.²³⁴ Each category reflects both the kind of evidence and the confidence in its reliability.²³⁵ Those categories are then used to further classify evidence. A “strong” recommendation is persuasive evidence from Level A.²³⁶ Clinically uncertain evidence—evidence from categories B or C—generates an “equivocal” rating.²³⁷ Finally, Lexi-Drugs recommends “against” a use when the evidence does not support it or suggests it is not effective or safe.²³⁸

The National Comprehensive Cancer Network (“NCCN”) also uses a rating system to group evidence into categories. Its rating system is based on determinations made in developing another tool for physicians: CPGs.²³⁹ NCCN’s CPGs make three recommendations, all of which it considers “appropriate”: “[p]referred [i]ntervention,” “[o]ther recommended intervention,” and “[u]seful in some circumstances.”²⁴⁰ Each category—1, 2A, 2B, and 3—corresponds to both the quality of the evidence and the level of internal consensus as to the clinical recommendation based on that evidence.²⁴¹ Category 1 is based on high quality evidence and is uniformly supported.²⁴² Here evidence means “high-powered randomized clinical trials or meta-analyses.”²⁴³ Category 2A is supported by lower quality evidence but the NCCN Guidelines Panel still uniformly supports it.²⁴⁴ Evidence can include anything from “phase II to large cohort studies . . . to case series to individual practitioner experience.”²⁴⁵ When there is “nonuniform consensus”—but not “major disagreement”—for a use supported by lower quality evidence, NCCN places it in Category 2B.²⁴⁶ NCCN reserves Category 3 for uses with “any” kind of

²³³ Lexi-Drugs Revision Request, *supra* note 226, at 5.

²³⁴ *Id.* at 5–6.

²³⁵ *Id.* at 8–9.

²³⁶ *Id.* at 8.

²³⁷ *Id.*

²³⁸ *Id.* at 9.

²³⁹ Email from Marian Birkeland, Senior Dir., Compendia Dev., Nat’l Comprehensive Cancer Network, to author (Sept. 17, 2020, 12:24 PM) (on file with author).

²⁴⁰ *Development and Update of Guidelines*, NAT’L COMPREHENSIVE CANCER NETWORK [hereinafter *NCCN Development*], <https://www.nccn.org/guidelines/guidelines-process/development-and-update-of-guidelines> (last visited Oct. 14, 2020).

²⁴¹ NCCN Revision Request, *supra* note 213, at 5–6.

²⁴² *Id.* at 5.

²⁴³ *Id.*

²⁴⁴ *Id.*

²⁴⁵ *Id.* at 5–6.

²⁴⁶ *Id.*

evidentiary support and “major disagreement” among NCCN panels, the groups of individuals that evaluate any given use.²⁴⁷

DrugDex uses a similar system. First, it rates the “Strength of Evidence” for each use, ranking evidence as Category A, B, or C.²⁴⁸ Evidence in Category A usually comprises meta-analyses with consistent conclusions and “[m]ultiple, well done randomized clinical trials involving large numbers of patients.”²⁴⁹ Category B evidence includes meta-analysis with conflicting results, randomized controlled trials with small numbers and methodological flaws, and nonrandomized studies.²⁵⁰ Evidence in Category C “is based on data derived from[] [e]xpert opinion or consensus [and] [c]ase reports or case series.”²⁵¹ Evidence strength is used to make decisions about the evidence of efficacy and the strength of recommendations.²⁵²

Second, using this framework, DrugDex purports to offer ratings about how effective a drug is and whether doctors should use it.²⁵³ The former is divided into classes I (“[e]ffective”), IIa (“[e]vidence [f]avors [e]fficacy”), IIb (“[e]vidence [i]s [i]nconclusive”), and III (“[i]neffective”).²⁵⁴ Judgments about the category into which evidence falls is based on the nature of the evidence “and/or expert opinion.”²⁵⁵ The final category into which uses are grouped is “Strength of Recommendation,” which is organized by “[s]trength” and relates to whether the drug is “useful.”²⁵⁶ Drugs in each class are: proven useful and should be used (Class I); “generally considered . . . useful, and is indicated in most cases” (Class IIa); useful and “indicated in some, but not most, cases” (Class IIb); and “not useful and should be avoided” (Class III).²⁵⁷

Gold Standard, Elsevier’s drug compendium, uses the “Grading of Recommendations Assessment, Development and Evaluation (GRADE) system,” which ranks evidence along four dimensions of quality: high,

²⁴⁷ *Id.*

²⁴⁸ DrugDex Revision Request, *supra* note 213, at 6–7.

²⁴⁹ *Id.* at 7.

²⁵⁰ *Id.*

²⁵¹ *Id.*

²⁵² *Id.*

²⁵³ *Id.* at 5, 8.

²⁵⁴ *Id.* at 6–7.

²⁵⁵ *Id.* “‘Thomson Micromedex’ classification is patterned after the widely accepted American College of Cardiology/American Heart Association and U.S. Preventive Services Task Force (USPSTF) guidelines.” *Id.* at 6.

²⁵⁶ *Id.* at 7.

²⁵⁷ *Id.*

moderate, low, and very low.²⁵⁸ Phase III RCTs appeared to be presumptively “high” quality, which can be “downgraded to a lower quality” for a variety of methodological reasons, “including publication bias.”²⁵⁹ When multiple studies exist, Elsevier evaluates overall quality using the studies with the worst quality evidence relating to the most important use.²⁶⁰ Once the evidence is assessed, Elsevier assigns a “grade” of “Strong” or “Equivocal/Weak” under the GRADE system.²⁶¹ “Strong” recommendations are either for or against uses.²⁶² Strongly recommended uses are “clearly identified as recommended or not recommended.”²⁶³ “Equivocal/Weak Recommendations” are “clearly identified as equivocal.”²⁶⁴ The difference between strong and weak recommendations is, at bottom, a cost-benefit analysis that factors in the price of non-treatment and alternative treatments.²⁶⁵

AHFS uses four evidence levels: “Level 1: High Strength/Quality;” “Level 2: Moderate Strength/Quality;” “Level 3: Low Strength/Quality;” and “Level 4: Opinion/Experience.”²⁶⁶ Each level is more granular than some of the other rating systems just explained,²⁶⁷ but overall the system’s thrust is similar. It uses these levels of evidence to grade its recommendations for particular uses.²⁶⁸ A “Recommended (Accepted)” grade applies when “[t]he drug or biologic should be used, is recommended/indicated, or is useful/effective/beneficial in most

²⁵⁸ *Elsevier Editorial Policy for Off-Label Data Within Drug Information Products and Databases*, ELSEVIER [hereinafter *Elsevier Editorial Policy*], <https://www.elsevier.com/clinical-solutions/drug-information/editorial-policy/off-label-data> (Mar. 5, 2015).

²⁵⁹ *Id.* (“[L]ower quality level[s] include study design flaws, inconsistent results from other studies, imprecise results (e.g., small patient numbers, wide confidence intervals), use of study endpoints that are disease focused vs. patient focused (e.g., overall response rate vs. overall survival, LDL cholesterol concentration vs. myocardial infarction or stroke), and other biases, including publication bias.”).

²⁶⁰ *Id.* (“[T]he studies with the lowest quality of evidence for the most critically important outcome will be used to assign the overall quality of evidence for the off-label use.”).

²⁶¹ *Id.*

²⁶² *Id.*

²⁶³ *Id.* But it will not ever recommend against. *Id.* (“[A] strong recommendation ‘Against use’ will not be found within the clinical decision support data.”).

²⁶⁴ *Id.*

²⁶⁵ *Id.* (“The strength of recommendation is primarily derived by evaluating the risks vs. benefits of the recommendation to the alternatives, the quality of the evidence, the variability in the importance of the risks and benefits to the patients and clinicians (i.e., an outcome that is important to most patients such as preventing a stroke vs. the inconvenience of warfarin in atrial fibrillation is more likely to receive a strong recommendation), and resources or costs of the intervention.”).

²⁶⁶ *Levels of Evidence Rating System*, AHFS CLINICAL DRUG INFO., <https://www.ahfsdruginformation.com/levels-of-evidence-rating-system/> (last visited Oct. 14, 2020).

²⁶⁷ *Id.* Evidence qualifies as “Level 2,” for example, if any of five non-exclusive criteria are met. *Id.*

²⁶⁸ *Id.*

cases.”²⁶⁹ This system was developed, AHFS says, by consulting a variety of medical and government literature.²⁷⁰

D. Limitations of Compendia: Inconsistency, Opacity, and Conflicts of Interest

Different evaluative frameworks also produce different evaluations. When, in 2007, MEDCAC (through the AHRQ) studied how compendia evaluated and rated fourteen oncology drugs for off-label uses, it found opaque and inconsistent evaluations.²⁷¹ Because of their opacity, however, no one could tell exactly *why* compendia reached different conclusions about the evidence for off-label uses.²⁷² Compendia editors, the study found, used “[s]ubjective” or “[p]rofessional” assessments to evaluate evidence; but *how* editors and experts made those decisions was not clear.²⁷³

One possible explanation for variation was the use of different inclusion criteria, terminology, and rating systems for off-label uses.²⁷⁴ Another was compendia’s ineptitude: they were quite bad at sourcing the information they claimed to be evaluating.²⁷⁵ When compendia did cite literature, it “was often neither the most recent nor the most valid in terms of study design.”²⁷⁶ All of these factors amounted to inconsistent assessments among compendia about whether and how to include various uses.

This may not be all the compendia’s fault. They may simply lack information. Unlike the FDA, compendia do not have access to unpublished

²⁶⁹ *Id.*

²⁷⁰ *Overview*, AHFS CLINICAL DRUG INFO., <https://www.ahfsdruginformation.com/off-label-uses-overview> (last visited Oct. 14, 2020) (“The development of the AHFS evidence rating system applied the principles of Fletcher and Sackett, as reflected most notably in the work of the American College of Chest Physicians (ACCP). FDA guidance documents for assessing clinical trials, levels of evidence applied by the Agency for Healthcare Research and Quality (AHRQ; formerly Agency for Health Care Policy and Research, AHCP) and ASHP’s Council on Therapeutics, as well as several dozen other documents and resources on evidence-based medicine were addressed as part of this process.”).

²⁷¹ *See generally* AHRQ 2007 COMPENDIA COVERAGE, *supra* note 204. Shortly before Congress passed legislation recognizing compendia as authoritative sources for reimbursement, several authors studied how compendia evaluated, and third-party payors reimbursed, off-label uses. Drusilla S. Raiford et al., *supra* note 199, at 45 (“Given the variability and the imprecise nature of the inclusion standards, and considering the differences in the depth and method of review, in the level of industry involvement, and in the mix of outside consultants, it should be expected that the end products will differ.”).

²⁷² AHRQ 2007 COMPENDIA COVERAGE, *supra* note 204, at 9, 11–14.

²⁷³ *Id.*

²⁷⁴ *Id.* at 8–9, 11–14, 108–09.

²⁷⁵ *Id.* at 19–20, 24–25, 31–32, 37, 42, 47, 54, 58–59, 65–66, 72, 80–81, 88–89, 96, 101, 106–07.

²⁷⁶ *Id.* at 107.

drug company research; they are usually reviewing only published research.²⁷⁷ Because published research is more likely to be positive, any compendium's survey of evidence is likely to reflect this publication bias.²⁷⁸ Regulatory review by the FDA or the CMS of the actual indications compendia include does not occur.²⁷⁹ So there is no backstop for publication bias. This is particularly troubling because pharmaceutical firms often have elaborate schemes to release and control publication results.²⁸⁰

Compendia could, as the subsequent 2009 AHRQ study found, combat publication bias using different mechanisms. First, when evaluating evidence, investigators should be mindful of "sponsor conflict of interest": conflicts of interest between the study authors and the sponsor(s) of the study.²⁸¹ Turning a skeptical eye toward industry-sponsored papers would certainly help.²⁸² As an added prophylactic, the report suggested including all data from ClinicalTrials.gov, not just published results.²⁸³

While the CMS has provided a framework for compendia to reduce these problems,²⁸⁴ there is no hard evidence about how, if at all, compendia are implementing these or other suggestions.²⁸⁵ NCCN, for example, states that its primary mechanism for literature collection searches only PubMed and, therefore, excludes all of the "unsuccessful" studies available in ClinicalTrials.gov.²⁸⁶ Gold Standard does not expressly include or exclude

²⁷⁷ AHRQ 2009 WHITE PAPER, *supra* note 188, at 23–24.

²⁷⁸ *Id.*; see Christopher W. Jones, Lara Handler, Karen E. Crowell, Lukas G. Keil, Mark A. Weaver & Timothy F. Platts-Mills, *Non-Publication of Large Randomized Clinical Trials: Cross Sectional Analysis*, 347 *BMJ* 1, 3, 7, 8 (2013) (finding 29% of all trials registered in ClinicalTrials.gov prior to January 2009 remained unpublished and the majority of those (78%) had no results available on ClinicalTrials.gov, and that 88% of all unpublished trials were industry funded).

²⁷⁹ Kevin W. Su, Cary P. Gross, Nicholas S. Downing, Kerin B. Anderson & Joseph S. Ross, *Cancer Therapeutic Clinical Trials Supporting FDA Approval and Compendia Inclusion*, 9 *AM. J. PHARM. BENEFITS* 122, 128 (2017) ("Furthermore, no external regulatory mechanisms currently exist to evaluate off-label therapeutic use endorsed by compendia.").

²⁸⁰ Lindsey Gabrielsen, *Bias at the Gate?: The Pharmaceutical Industry's Influence on the Federally Approved Drug Compendia*, 40 *AM. J. L. & MED.* 141, 157–58 (2014).

²⁸¹ See AHRQ 2009 WHITE PAPER, *supra* note 188, at 21–22 ("Relevant information for assessing potential conflict of interest includes the identification of the sponsor, determination of whether an independent team reviewed the raw data, and determination of whether conclusions were formulated independent of sponsor interests." (emphasis omitted)).

²⁸² See *id.* at 22, 58.

²⁸³ *Id.* at 25.

²⁸⁴ See *supra* note 281 and accompanying text.

²⁸⁵ My requests to compendia for information were either rejected or ignored.

²⁸⁶ *NCCN Development*, *supra* note 240 ("Specific information regarding the literature search for any of the Guidelines can be found at the beginning of the Discussion section in each Guideline.").

“unpublished” reports or trial data in its list of included information sources.²⁸⁷ Lexi-Drugs²⁸⁸ and AHFS have similar policies.²⁸⁹

Compendia, however, are not totally indiscernible. They do publish information about their decision-making processes—but the key nuts and bolts of this process still remain opaque.²⁹⁰ And their opacity results partly from their business model. A large portion of compendia’s constituency comprises the pharmaceutical sector. This, in turn, produces another incentive: to cater to the pharmaceutical companies whose drugs they include in their compendia.

Conflicts of interest—conflicts that influence either investigator data selection or data interpretation²⁹¹—could present serious problems for compendia.²⁹² Pharmaceutical companies can make this problem worse by increasing the likelihood that review of a particular use is requested. All they have to do is request compendia review their drugs/uses or publicize them to doctors.²⁹³ The former increases the chances that the compendia include the drug/use; the latter increases the likelihood that a physician will initiate a request for compendia review in response to the information provided by the drug company.²⁹⁴

Although some compendia had conflict-of-interest policies, they also left evaluation of evidence to investigators’ discretion. What constituted a “good” study—one that played a role in an inclusion determination—at each

²⁸⁷ *Elsevier Editorial Policy*, *supra* note 258 (stating that among the sources it considers are published studies, which it lists as the primary literature, national practice guidelines, “other accepted sources of medical information (e.g., FDA, CDC, NIH communications),” and “[d]ialogue with customers or other external reviewers of our content”).

²⁸⁸ Lexi-Drugs Revision Request, *supra* note 226, at 4 (“An internal surveillance team identifies prescribing information changes as well as changes from primary literature and clinical practice guidelines on a daily basis. Other updates are identified through peer reviewed journal surveillance, routine internal monograph review and updating, an external panel of senior editors and consultants who practice within healthcare systems in the US, and unsolicited client questions.”).

²⁸⁹ *Overview*, AHFS CLINICAL DRUG INFO., <https://www.ahfsdruginformation.com/off-label-uses-overview> (last visited Oct. 14, 2020) (noting it considers “published reports of well-designed clinical studies” but not specifically excluding “unpublished” reports).

²⁹⁰ While information about the general process of decision-making is available online, the actual decision-making process, including the rationales of the decisionmakers, of drug inclusion is not.

²⁹¹ AHRQ 2009 WHITE PAPER, *supra* note 188, at 19.

²⁹² *See generally id.*; Robert W. Carlson, *Industry “Rewrites” of NCCN Guidelines*, 9 J. NAT’L COMPREHENSIVE CANCER NETWORK 257, 257 (2011).

²⁹³ *E.g.*, *Elsevier Editorial Policy*, *supra* note 258 (“The Elsevier drug information editorial team will review external requests to add off-label indication information. External requests are handled in the same manner as those indications identified through the internal review processes.”).

²⁹⁴ AHRQ 2009 WHITE PAPER, *supra* note 188, at 24–25. It should be noted that, under my proposal, this practice will be limited by the evidentiary rating system itself. *See infra* Part III.

compendium was determined by the subjective judgment of a reviewer or investigator.²⁹⁵ That subjective judgment, even for compendia that are nonprofit, can be significantly compromised by financial conflicts of interest.²⁹⁶ Investigators, outside experts, or even the compendia themselves can have financial interests related to the drugs and uses they are reviewing. One compendium compounded, rather than ameliorated, the problem by promising expedited review for a fee of \$50,000.²⁹⁷

Despite the dangers posed by financial ties, *some* conflict of interest is inevitable because there are a limited number of both reviewing entities and reviewers with the relevant expertise.²⁹⁸ The question is how to manage these conflicts of interest. Although the CMS has issued guidelines that generally address this area, compendia have significant leeway to comply. NCCN, for example, has a conflict-of-interest policy, but a conflict of interest does not necessarily disqualify participation in decision-making.²⁹⁹ That decision is left to Panel Chairs, who are notified of the conflict by NCCN Staff.³⁰⁰ And the sanctions for violating this policy are limited to the only recourse the compendium has: removing the offending party from participation.³⁰¹ Micromedex, which publishes DrugDex, has a tiered conflicts policy that requires disclosure, but allows participation for individuals with conflicts of less than \$100,000.³⁰²

²⁹⁵ *Id.* at 25.

²⁹⁶ *Id.* at 32–33 (noting NCCN, the only nonprofit of the recognized compendia, had significant conflicts of interest). Large corporate entities, such as Thomson, which owns DrugDex, also offer a variety of database and healthcare products. Those entities can have financial ties that create conflicts of interest. The same is true for new databases, such as Lexi-Drugs.

²⁹⁷ *Id.* at 30–31, 41–42. This is not a problem limited to compendia. The FDA faces a similar conflict under the 1992 Prescription Drug User Fee Act (PDUFA), Pub. L. 102-571, 106 Stat. 4491 (codified at 21 U.S.C. §§ 379g, 379h (1994)).

²⁹⁸ AHRQ 2009 WHITE PAPER, *supra* note 188, at 40 (“Conflict of interest is an acknowledged, and largely unavoidable, factor in the development of drug compendia due to the nature of inputs to the process (data on drug effectiveness, safety, toxicity, and use, which requires selection and interpretation), the parties involved in the process (individuals with various relationships to drug manufacturers), and outcomes of the process (listing in a compendium, which has financial implications).”).

²⁹⁹ See *NCCN Disclosure Policies and Potential Conflicts of Interest*, NAT’L COMPREHENSIVE CANCER NETWORK art. III, <https://www.nccn.org/guidelines/guidelines-panels-and-disclosure/disclosure-policies-and-potential-conflicts-of-interest> (last visited Oct. 14, 2020).

³⁰⁰ *Id.*

³⁰¹ *Id.* at art. IV.

³⁰² IBM WATSON HEALTH, CONFLICT OF INTEREST POLICY FOR IBM MICROMEDEX 3 (2019), <https://www.ibm.com/downloads/cas/8WBZ9KAJ>. There are some additional subtleties—such as barring participation by a pharmaceutical employee during their employment and for 6 months after leaving—which one can read about in the policy.

As the 2009 MEDCAC Study noted, disclosure of conflicts does not solve the problem. Practitioners and payors who use compendia are unlikely to interpret the data in light of the primary sources, even if they have conflicts information.³⁰³ For payors, in particular, disclosures are irrelevant: inclusion usually means payment.³⁰⁴

Not all of the news was bad, however. Compendia did an acceptable job describing toxicity and adverse events.³⁰⁵ But, as noted above, the concerns were great enough that the CMS promulgated the MEDCAC Characteristics and 2009 Admission Criteria for compendia. These requirements forced compendia to make at least some changes, though it is not clear how effective these changes have been.

Policies that are not implemented are just words. And there is evidence that compendia do a great deal of talking.³⁰⁶ Compendia publish data about conflicts, but not about removal or sanctions.³⁰⁷ Because the CMS has no mechanism in place to review whether and how these policies are working, the government has not examined how closely compendia now hew to the representations they made when requesting addition.

And it does not seem to have any immediate plans to do so. All but one of the recognized compendia were approved in 2009, and have not been reviewed since. The CMS's most recent addition of Lexi-Drugs in 2015 followed the same template as the 2009 approvals. And the CMS has made no effort to engage in substantive review of implementation.³⁰⁸ Calls to implement and prospectively evaluate more rigorous and systematic conflicts policies and procedures have gone unheeded.³⁰⁹

Recent work on compendia consistency and reliability is equivocal. One study, for example, found wide variability in both ratings and inclusion of off-label indications for atypical antipsychotics, with “many [of those included]

³⁰³ AHRQ 2009 WHITE PAPER, *supra* note 188, at 50–51.

³⁰⁴ The CMS must reimburse oral cancer treatments that appear in recognized compendia. But there may be conditional payment for off-label uses reimbursed by private payors. Cohen, Wilson & Faden, *supra* note 198, at 394–96. Often, payors, including the CMS, do not know the use is off-label.

³⁰⁵ AHRQ 2007 COMPENDIA COVERAGE, *supra* note 204, at 110.

³⁰⁶ As the 2009 White Paper notes, “the present study underscores the fact that compendia’s stated policies do not necessarily reflect the realities of their implementation.” AHRQ 2009 WHITE PAPER, *supra* note 188, at 44.

³⁰⁷ Email from Kristina Gregory, Vice President, Clinical Info. Operations, Nat’l Comprehensive Cancer Network, to author (Sept. 17, 2020, 10:08 AM) (on file with author).

³⁰⁸ See *WK Decision Letter*, *supra* note 216.

³⁰⁹ AHRQ 2009 WHITE PAPER, *supra* note 188, at 44.

unsupported by RCT evidence.”³¹⁰ It also found that compendia routinely favored off-label uses of new atypical antipsychotics to older typical antipsychotics for *reasons unrelated to the quality or quantity* of evidence supporting the uses.³¹¹

A more recent study, however, suggests that at least one compendium’s (DrugDex) recommendation of off-label indications, in at least one area (cancer), was based on evidence that is consistent with the kind of evidence the FDA relies on to approve supplemental indications (“SNDAs”).³¹² The same study, however, noted that the quality of evidence needed for a supplemental indication was likely higher than that needed for inclusion in DrugDex.³¹³

In 2017, a different group of researchers compared compendia entries concerning off-label uses for the cancer drug erlotinib.³¹⁴ Similar to the 2007 White Paper, the 2017 publication found “[p]ersistent inconsistencies . . . in recommendations between the compendia and methodological weaknesses in the analyses of the evidence.”³¹⁵ Some compendia listed one off-label use while another listed eight.³¹⁶ The evidentiary support was weak for several of these indications.³¹⁷ Another study of cancer drugs found similar problems with the evidence cited to support off-label uses.³¹⁸

Compendia are not perfect. And there is still much we do not know about how they operate. But they do provide an underutilized source of information about off-label uses and the evidence supporting them. They also are subject to regulation by the CMS. And past regulation demonstrates that compendia have incentives to comply with these regulations and will make significant efforts to

³¹⁰ Richard P. Paczynski, G. Caleb Alexander, Vernon M. Chinchilli & Stefan P. Kruszewski, *Quality of Evidence in Drug Compendia Supporting Off-Label Use of Typical and Atypical Antipsychotic Medications*, 24 INT’L J. RISK & SAFETY MED. 137, 139 (2012).

³¹¹ *Id.* at 142–43.

³¹² Su et al., *supra* note 279, at 127–28. This study had several limitations, including not identifying the quality of evidence “other than trial design, such as effect sizes or safety.” *Id.* at 129. The authors, it should be noted, disclose several financial conflicts of interest, including funding from Johnson & Johnson, Blue Cross Blue Shield Association, Medtronic, Inc., and the Laura and John Arnold Foundation. *Id.*

³¹³ *Id.* at 128.

³¹⁴ Angela K. Green, William A. Wood & Ethan M. Basch, *Time to Reassess the Cancer Compendia for Off-label Drug Coverage in Oncology*, 316 JAMA 1541, 1541 (2016).

³¹⁵ *Id.*

³¹⁶ *Id.*

³¹⁷ *Id.*

³¹⁸ Jeffrey Wagner, John Marquart, Julia Ruby, Austin Lammers, Sham Mailankody, Victoria Kaestner & Vinay Prasad, *Frequency and Level of Evidence Used in Recommendations by the National Comprehensive Cancer Network Guidelines Beyond Approvals of the US Food and Drug Administration: Retrospective Observational Study*, 360 BMJ 1, 5 (2018).

do so. The next Part explains how to improve compendia and use them to tie regulation of off-label information to the level of evidence supporting the relevant off-label use.

III. TYING INFORMATION TO EVIDENCE

Although compendia have shortcomings, they provide information about drugs, their uses, effects, safety, and evidence base. Importantly, they rank off-label uses according to the quality and quantity of evidence supporting them. The FDA could leverage this information to regulate off-label promotion, an area it has struggled to police.

There are five ways that the FDA could use compendia to link regulations of information about off-label use to evidence. First, it could simply apply the CMS's reimbursement framework to regulations concerning off-label information. Second, the FDA could use CMS-recognized compendia but regulate them indirectly by specifying the level of evidence required for a specific informational activity. Third, the FDA could regulate compendia both directly (by specifying criteria necessary to be a "recognized" or "official" FDA compendia) and indirectly (by specifying the level of evidence required for a specific informational activity). Fourth, the FDA and the CMS could collaborate on one framework for both direct and indirect regulation. Finally, the FDA could collaborate with the CMS to regulate compendia directly but separately regulate them indirectly.

Sections A and B, below, sketch how each proposal might work, and why the fifth method for using compendia—where the FDA and the CMS collaborate to regulate compendia directly and each separately regulates them indirectly—is preferable. In all of these approaches, however, the regulations would function identically and in two steps. First, they would mandate that off-label informational activities be linked to the "specified evidence base" for a use as stated in "recognized" compendia. Second, the regulations would explain the kind, quantity, and nature of informational activities permitted given the specified evidence base. After explaining how each approach might function, Section C illustrates the proposal using three examples.

A. *Using Compendia off the Shelf: No or Indirect Regulation*

The first option is the cheapest and easiest: use currently recognized compendia to tie off-label information dissemination to evidence. Even here, however, there are possible variations for how to implement this proposal.

Recall that the CMS covers drugs only for “medically accepted indications.”³¹⁹ Drugs and uses appearing in recognized compendia on the terms set by the CMS, as a matter of law, satisfy this standard.³²⁰ For cancer drugs, the CMS recognizes five compendia for reimbursement purposes.³²¹ For all off-label uses, only two make the list.³²²

Because compendia employ different evidentiary rating systems “that may not be readily cross-walked” from one to the other, simply *appearing* in a single compendium will not guarantee reimbursement.³²³ The CMS has rules about what kind of variation matters. Cancer drugs can be reimbursed if any one of the following is true:

1. NCCN lists the drug as Category 1 or 2A;
2. DrugDex lists the drug in Classes I (effective), IIa (evidence favors efficacy), or IIb (evidence is inconclusive);
3. Lexi-Drugs lists a drug as “Off-Label” and rates the evidence supporting the use as Level A; or
4. AHFS-DI or Clinical Pharmacology have supportive “narrative text.”³²⁴

If, however, *any* compendium rates a drug as “unsupported, not indicated, not recommended, or equivalent terms,” then prescription drug plans (“PDPs”) can deny coverage.³²⁵

Non-cancer drugs are treated differently. Recall that for non-cancer drugs, there is a different statutory list of recognized compendia: AHFS-DI and DrugDex.³²⁶ That list has not undergone any changes—no compendia have requested additions and the CMS has not sought to remove any. Although the list of compendia for Part D off-label uses is smaller than the one for cancer drugs, CMS will reimburse when “the use of [a drug] is supported by one or

³¹⁹ MEDICARE BENEFIT POLICY MANUAL, *supra* note 192, § 50.4.5.

³²⁰ *Id.*

³²¹ *Id.*

³²² MEDICARE PRESCRIPTION DRUG BENEFIT MANUAL, *supra* note 195.

³²³ MEDICARE BENEFIT POLICY MANUAL, *supra* note 192, § 50.4.5.

³²⁴ *Id.* “The complete absence of narrative text on a use is considered neither supportive nor non-supportive.” *Id.* Contractors can request “[c]ompendia documentation or peer-reviewed literature supporting [the] off-label use.” *Id.*

³²⁵ *Id.* The statute seems to require this, though the Manual is not definite. 42 U.S.C. § 1395x(t)(B)(ii)(I).

³²⁶ MEDICARE PRESCRIPTION DRUG BENEFIT MANUAL, *supra* note 195.

more citations included or approved for inclusion in any of the compendia.”³²⁷ PDP sponsors—insurance companies that administer Part D insurance coverage to patients—“must reference all CMS recognized compendia to determine whether there are any supportive citations[] prior to determining that a drug is not being used for a medically-accepted indication.”³²⁸ The CMS also does not view drug dosage different from the labeled indication as an off-label use.³²⁹ Whatever the reasons for this difference and others,³³⁰ Part D off-label uses are subject to different reimbursement screening than cancer drugs.³³¹

1. No Regulation: Use the CMS Reimbursement Rules

One proposal simply applies this framework to off-label information. Covered drugs could be disseminated consistent with the FDA regulations; uncovered drugs could not, or would be treated the same as off-label promotion and/or dissemination are now. The FDA, of course, would have to issue regulations about what kind of information dissemination is permissible for covered uses.³³² But the framework is fairly straightforward.

This approach offers two advantages. The most obvious is the low cost of implementation. Because the FDA would simply be issuing regulations that corresponded to the current off-label reimbursement framework, implementing the approach would be relatively painless. For non-cancer off-label drugs, the FDA might need to do some occasional legwork. But it could also consider simply conferring with the CMS to evaluate how sponsors have reimbursed off-label uses.³³³

The other advantage is a more nuanced approach to off-label information dissemination. The FDA could retain existing carve-outs for reprints, articles,

³²⁷ *Id.*

³²⁸ *Id.* (emphasis omitted).

³²⁹ *Id.* (“Also, medically-accepted indication refers to the diagnosis or condition for which a drug is being prescribed, not the dose being prescribed for such indication. Part D sponsors may have dose limitations based on FDA labeling, but an enrollee may request (and be granted) an exception to a dose restriction through the formulary exception process based on medical necessity criteria.” (emphasis omitted)).

³³⁰ There is even a special rule for erectile dysfunction drugs. *Id.* § 20.1. The CMS will reimburse them only when they are prescribed for FDA-approved indications other than sexual or erectile dysfunction. *Id.* But it will not reimburse for off-label uses even if they appear in one of the two recognized compendia. *See id.*

³³¹ The reasons are tied to a variety of factors, including lack of diagnostic codes and utilization management techniques. Simon, *supra* note 172, at 25.

³³² This is not what Epstein suggests in passing. He would, it seems, totally deregulate—that is, allow *all* kinds of promotion typically allowed for approved drugs—off-label uses covered by Medicare. *See* Epstein, *supra* note 16, at 19–20, 33–34.

³³³ This would simply require information sharing, but not necessarily active collaboration. *See* Sachs, *infra* note 343, at 2017–27.

reference texts, and CPGs. But in the process, it would create a three-tiered system of regulation. In this system, labeled uses would be regulated as they have been—covered off-label uses would be regulated less strictly and the remaining uses would be regulated in the same way information about off-label use is regulated presently.

Although this system is cheap, the regulation is not very nuanced. All covered uses fall in the same evidentiary category. Informational regulation that tracks this system will make identical blunt judgments with respect to information dissemination. Since the reimbursement rules are largely binary, a use that is strongly supported might be promoted just as much as a use that is equivocal. Virtually any non-cancer off-label use listed in an official compendium will be reimbursed *even with a weak* evidence base for its use. Perhaps just as fatally, this proposal relies on the compendia system as it exists to regulate industry. And, as we have seen, that system faces significant challenges to produce reliable and accurate information.

Beyond these problems, however, this proposal effectively eliminates the FDA's authority to regulate the system upon which it is relying—a key point if the FDA is supposed to decide what drugs are safe and effective. And the FDA's core mission in this respect is different from the CMS's. The FDA is concerned with whether drugs are safe and effective, not whether they are prescribed for a medically accepted indication (or whether they are “reasonable and necessary”).³³⁴ Those two legal standards translate to different functions. While the CMS is responsible for reimbursement, the FDA is responsible for determining drug safety and efficacy.³³⁵ When the FDA does the latter, it is doing something different than when the CMS does the former. For all of these reasons, this approach is probably not the preferred one if better options are available—and they are.

2. *Indirect Regulation: Use New Evidentiary Ratings*

A second proposal would use existing compendia but regulate promotion *indirectly* based on their evidentiary ratings. Recall that the CMS regulates compendia directly through admission criteria and indirectly through reimbursement criteria.³³⁶ Under this approach, the FDA could accept the former but reject the latter for information about off-label uses. It could defer to the

³³⁴ 42 U.S.C. § 13957(a).

³³⁵ In another paper, I argue that the CMS has effectively become a mini- or secondary-FDA, creating a two-tiered and disjointed system of drug regulation. See Simon, *supra* note 172, at 14.

³³⁶ See *supra* Section II.B.

CMS on which compendia are authoritative but specify its own evidentiary criteria for various kinds of off-label informational dissemination. Each evidentiary grade in compendia would correspond to a different level of off-label information activity.

Like the proposal outlined above, this approach would be relatively efficient. Because the CMS already screens compendia, the FDA's only task would be to evaluate the evidentiary ratings and tie them to information-dissemination regulations. And it could do so without evaluating the evidence for each use. Once this task is complete, the FDA's role would be to enforce its regulations.³³⁷

Unlike the previous proposal, however, this one is more nuanced. Because each compendium rates uses differently, the FDA would need to specify the kinds of permissible off-label informational activity for each evidentiary grade in each compendium. That requires evaluating each compendium's evidentiary rating system. A drug, for example, may be rated as Category A by DrugDex, Category 2B by NCCN, and Level 2 by AHFS.

A variety of different rules could govern how much information dissemination is allowed in this situation. One rule might allow maximum off-label dissemination for the lowest rating in any compendium in which the use appeared. In this example, that would be either NCCN's category 2B or AHFS Level 2. An alternative rule could allow the maximum off-label information dissemination for the highest rating for the use in any compendium. Whatever rule the FDA chooses, it will have to individually evaluate compendia and their rating systems to craft its regulation. Its assessment of compendia reliability will be crucial to ensuring that the link between information dissemination and evidence is both tight and accurate.

Within this system, the FDA could still use existing Guidance as a framework for promulgating regulations or issuing new guidance documents. This framework may, in fact, eliminate the need for more regulation. One of the FDA's concerns, for example, is that CPGs may not be trustworthy.³³⁸ Many of the concerns that undergird trustworthiness—systematic review of evidence, qualified experts, transparent funding process, constant revision process—are the same concerns that undergird the CMS's regulation of compendia.³³⁹

³³⁷ It might consider revising the rules periodically to keep the compendia honest, but it is not clear how useful that process would be.

³³⁸ See IOM REPORT, *supra* note 75, at 34–36.

³³⁹ Compare FDA GUIDANCE: SCIENTIFIC & MEDICAL PUBLICATION, *supra* note 64, at 14–15 (describing desirable qualities for information), with Medicare Program Revisions, 72 Fed. Reg. 66222, 66304 (Nov. 27,

The FDA could avail itself of these criteria when it allows drug manufacturers to distribute CPGs. And it could allow *that* distribution—the distribution of conforming or non-conforming CPGs—only when a certain evidentiary threshold was met in a given compendium.³⁴⁰ Or it could allow greater kinds of dissemination activities of less trustworthy guidelines where the evidence is uniformly strong and allow distribution of the more trustworthy practice guidelines where the evidence is weaker. Alternatively, it could simply permit manufacturers to distribute only CPGs published by recognized compendia. Some mix of these approaches is also possible.

But given that CPGs *themselves* often provide a level of evidence for support—which does not necessarily follow any compendium’s process for grading evidence—it would be best not to rely on multiple evaluative sources.³⁴¹ The point is not to specify what approach is optimal, only to highlight that the existing FDA Guidance can be folded into any new system of evidence-based information regulation.

While this proposal is more nuanced than the one discussed above, it is also more expensive. But there may be good reasons for the added cost of devising a new evidentiary rating system for off-label information regulation. This, again, goes to the core function of the FDA, which, unlike the CMS, is in the business of regulating safety and efficacy, not reimbursement. While functionally similar, they are two distinct roles. Medicare may want to ensure patient access to drugs; the FDA may want to restrict the use of medications with little evidentiary support. So, if the FDA wants to promote truthful information about off-label uses, it should not rely on the CMS’s framework, which is designed to do something different. It would be perfectly reasonable for the FDA, after

2007) (to be codified at 42 C.F.R. §§ 409–11, 413–15, 418, 423–24, 482, 483–85) (stating MEDCAC characteristics).

³⁴⁰ Some compendia produce their own CPGs, which are based on the information in the compendia. *E.g.*, Email from Marian Birkeland, Senior Dir., Compendia Dev. Nat’l Comprehensive Cancer Network, to author (Sept. 17, 2020, 12:24 PM) (on file with author).

³⁴¹ *E.g.*, Glenn N. Levine, Eric R. Bates, John A. Bittl, Ralph G. Brindis, Stephan D. Fihn, Lee A. Fleisher, Christopher B. Granger, Richard A. Lange, Michael J. Mack, Laura Mauri et al., *2016 ACC/AHA Guideline Focused Update on Duration of Dual Antiplatelet Therapy in Patients With Coronary Artery Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines: An Update of the 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention, 2011 ACCF/AHA Guideline for Coronary Artery Bypass Graft Surgery, 2012 ACC/AHA/ACP/AATS/PCNA/SCAI/STS Guideline for the Diagnosis and Management of Patients With Stable Ischemic Heart Disease, 2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction, 2014 AHA/ACC Guideline for the Management of Patients With Non-ST-Elevation Acute Coronary Syndromes, and 2014 ACC/AHA Guideline on Perioperative Cardiovascular Evaluation and Management of Patients Undergoing Noncardiac Surgery*, 134 *CIRCULATION* 123, 126–27 (2016).

reviewing the evidence rating for each compendium, to decide some reimbursed uses should not be disseminated as widely as others.

While the increased nuance may be worth the added cost, this system has another shortcoming: it will not work well for drugs the CMS does not reimburse. If a drug is not covered, then a firm that disseminates information about the use may spend money on consumers who cannot pay. That is not a particularly good strategy. Firms are, therefore, most likely to expend advertising dollars on covered uses. This would make any rating system effective only as to covered uses. While this is somewhat problematic, it is not especially concerning for two reasons. First, the FDA could still attempt to police these informational activities with its existing safe harbors. Second, the number of uses to be missed are likely to be small.

More problematic, however, is the fact that using existing compendia means accepting the CMS's determination about what compendia are authoritative. As noted above, the core missions of the CMS and the FDA are different. And the FDA may have a different vision than the CMS about what constitutes acceptable review and rating of evidence. The FDA is also unlikely to kowtow to the CMS. But potential agency conflict is not a reason to abandon the proposal; it is a reason for agencies to collaborate to ensure it works.

B. Regulating Compendia

Since indirect regulation is cheap but less effective than direct regulation, the FDA's other choice is to regulate compendia directly. This would involve the FDA "recognizing" compendia for the purposes of advertising when they meet certain criteria. Here there are two basic strategies. The first is for the FDA to go it alone and issue its own regulations for official compendia. The other is to collaborate with the CMS to develop more comprehensive standards that serve both agencies' goals. Section 1 reviews the former; Section 2 the latter. Given that both agencies' goals overlap substantially, this Part concludes that collaborative regulation of compendia is the preferable approach.

1. Regulation by the FDA Alone

To regulate compendia directly, the FDA could issue regulations articulating criteria that compendia must meet for them to be "recognized" FDA

compendia.³⁴² The FDA could then issue indirect regulations like those discussed above: the level of permissible informational activity would correspond to the evidentiary support for each use in each compendium. To implement this approach, the FDA would need to develop a set of criteria that produced reliable and accurate evidence.

Because the FDA is concerned with safety and efficacy, it is likely to articulate more stringent requirements for inclusion and evidence ratings than the CMS. At the same time, however, the CMS and the FDA do share a common goal: to make compendia more reliable and transparent. The FDA's approach to compendia, then, should address their existing shortcomings: variability, opacity, and unreliability.

Issuing guidance or regulations to address these shortcomings opens two possible paths for the FDA. One is to operate a system similar to the CMS, where compendia can apply for "recognized" status. This system could either be competitive and exclusive (only one compendium could win) or competitive and nonexclusive (the FDA would recognize any compendia that apply and meet the criteria).

The other option is to issue guidance stating the criteria compendia must adhere to without making official determinations about which compendia meet them. This would be similar to its existing Guidance for CPGs. There are two significant drawbacks of this approach, both discussed above in the context of CPGs. First, guidance documents are not official law, and they would have uncertain legal status—especially given the FDA's recent judicial defeats. More importantly, however, is that this would not do much to regulate compendia. Unless the FDA vetted every existing compendium, it would enforce these rules only in specific instances. In each instance, it would have to show that the compendia relied on by the drug manufacturer did not meet its criteria. If, on the other hand, the FDA is going to evaluate every potential compendium, it should at least narrow the field and require applicants to submit information to *it*, rather than the other way around.

2. *Regulation by Collaboration between the FDA and the CMS*

While the FDA could act alone, doing so would come at considerable cost. Not only would the FDA need to devise an entirely new system for regulating

³⁴² In its strongest form, Congress would specify the FDA's authority to regulate similar to how it provided authority to CMS. Congress, however, has not yet done so, raising a host of administrative law questions. While interesting, these questions are beyond the scope of this Article.

compendia, it would also need to regulate them. Here the FDA has the competency but lacks experience. Because the CMS has an established record of regulating compendia—including studying their deficiencies and addressing them through regulation—collaboration between the CMS and the FDA makes more sense than a new regulatory regime.³⁴³

Two other reasons support a collaborative, rather than siloed, approach. First, there is a mutuality of interests despite the difference in legal obligation: both the CMS and the FDA want accurate and reliable assessments of evidence supporting off-label uses. While the CMS uses this information to make reimbursement decisions, the FDA will use it to make decisions about promotion. Ultimately, the CMS and the FDA may decide to invoke different *indirect* regulation—they may set different evidentiary thresholds for reimbursement or permissible informational activity. Given that their interests diverge, as mentioned above, this Article argues they *ought* to impose different indirect regulation. Despite this difference, however, the type and quality of information needed for both activities—regulating information dissemination based on safety and efficacy and regulating reimbursement—is largely the same. And the best way to obtain that information is by common, direct regulation.

A second reason for the FDA to partner with the CMS is practical: the latter has the statutory authority to regulate compendia. While the FDA's ability to regulate off-label promotion has been challenged, the CMS's approach to regulate compendia has not. And the FDA's ultimate position on *off-label information dissemination*—whether in regulation or in official guidance—need only incorporate rules for compendia set by the CMS. This means that challenges to the FDA's evidence-based regime could not attack the underlying rating mechanism itself, shielding the collaborative efforts from total legal destruction.³⁴⁴ Although the FDA's regulations of off-label information may fall, the framework it built with the CMS to regulate compendia will remain.

While there are several choices about how the CMS and the FDA would collaborate—each of which may have legal implications—this Article does not explore them here. Nor does this Article explore the precise contours of the FDA's indirect regulation (which this Article partially addresses in the following section), or how it might differ from the CMS's indirect regulation. Instead, this

³⁴³ See Rachel E. Sachs, *Administering Health Innovation*, 39 CARDOZO L. REV. 1991, 2016–26, 2036–38 (2018) (describing three types of collaboration—information sharing, research, and decision-making—and the relative costs and benefits of each, and also noting collaborations between the CMS and the FDA).

³⁴⁴ The FDA's *indirect* regulation could be challenged and invalidated. But that would not jeopardize the underlying direct regulation, which is within the purview of CMS to promulgate and enforce.

Article focuses on what the general collaboration would look like, including its goal: to improve compendia transparency, reliability, and variability.

To increase transparency, the direct regulation should force compendia to publish more information about most of what they do, including how and when they decide to identify and evaluate evidence, according to what standards, and their rationale for evaluating it. This should include a list of employees, and their qualifications, who identify new uses for inclusion, field requests for inclusion, and identify and evaluate evidence of uses considered for inclusion. Compendia should also publish information about all conflicts of interest, when the compendium disqualified reviewers, what actions were taken, when sanctions were imposed, etc.

Simply making more information public, of course, will not make compendia more reliable or uniform. Part of the reason is because it is not clear that compendia have standardized processes for many of the activities that drive their unreliability and variability. Currently compendia have various practices for identifying, gathering, and evaluating information about a drug use—as well as the form in which they present this information. Just how variable these are—and how much discretion compendia exercise—is difficult to know because compendia refuse to disclose this information.³⁴⁵ These systems leave to compendia significant discretion to make decisions about when, where, and how to look at, or for, evidence. They also allow significant discretion to decide when evidence meets a threshold worthy of a given rating—ratings that are not uniform across compendia.

To reduce the role and distortions of subjective assessments, direct regulation must standardize these processes. Regulations would *require* compendia to standardize conflict-of-interest policies and procedures, as well as the processes compendia use to initiate, evaluate, and rate evidence for off-label uses. This would, at a minimum, also require compendia to detail the information flows for every potentially evaluated use, including the parties making assessments and the algorithms they use to do so. Forcing all compendia to use the same system for identifying, evaluating, and presenting evidence will narrow the range of permissible subjective judgments. And it will also highlight why different compendia reach different evidentiary decisions.

Although it seems difficult, it is possible to establish various “checkpoints” in the process that can be backstopped by objective criteria. Consider the

³⁴⁵ Email from Marian Birkeland, Senior Dir., Compendia Dev., Nat'l Comprehensive Cancer Network, to author (Nov. 18, 2020, 10:35 AM) (on file with author).

identification phase, when a compendium evaluates whether it should consider adding any particular use. Under the existing CMS framework, compendia are not required to implement a standardized process for identifying and vetting new uses for inclusion. And, as a result, they do not. NCCN, for example, considers changes to its compendium using three mechanisms: institutional review, internal literature review, and submission requests.³⁴⁶ But the process by which each of these occurs is not clear. The same can be said of other compendia.³⁴⁷

This raises both the prospect of inconsistency and the specter of bias. As to the former, compendia that employ different methodologies in how they choose (e.g., relying primarily on in-house staff versus outside experts) can produce different results (e.g., broader inclusion of uses versus those based on need). As to the latter, bias can arise because pharmaceutical companies may engineer requests for addition, either directly or indirectly through physicians. If pharmaceutical companies are making more requests (or cause others to make more requests) for their own pioneer drugs than generics, for example, then compendia may skew toward including uses requested by pharmaceutical companies.

Compendia also use various “monitoring” techniques to identify off-label uses. Some say little about how they monitor off-label data or how they decide to research a use further. Gold Standard (Elsevier), for example, performs a “regular and comprehensive review of[] [p]rimary published literature[,] [n]ew or updated national practice guidelines[,] [s]urveillance of other accepted sources of medical information (e.g., FDA, CDC, NIH communications)[] [and] [d]ialogue with customers or other external reviewers of [its] content, particularly practioners [sic] within the specialty field.”³⁴⁸ Lexi-Drugs (Wolters Kluwer) identifies off-label oncology uses by “[m]onitoring of [the National Library of Medicine’s] 119 premier/core journals[:]; [u]nbiased evidence-based clinical practice guidelines[:]; [c]lient request[:]; [e]xternal/[i]nternal request generated from drug monograph review[:]; [s]urvey of drug information centers,

³⁴⁶ *NCCN Development*, *supra* note 240. It uses the same rules for compendia updates. *E.g.*, Email from Marian Birkeland, Senior Dir., Compendia Dev., Nat’l Comprehensive Cancer Network, to author (Sept. 17, 2020, 12:24 PM) (on file with author).

³⁴⁷ Lexi-Drugs, for one, explains:

An internal surveillance team identifies prescribing information changes as well as changes from primary literature and clinical practice guidelines on a daily basis. Other updates are identified through peer reviewed journal surveillance, routine internal monograph review and updating, an external panel of senior editors and consultants who practice within healthcare systems in the US, and unsolicited client questions.

Lexi-Drugs Revision Request, *supra* note 226, at 4.

³⁴⁸ Clinical Pharmacology Revision Request, *supra* note 213.

list servs, or managed healthcare databases[;] [and] [h]ospital policies for trending prescribing patterns.”³⁴⁹ Lexi-Drugs also has inclusion criteria for literature searches, though it is not clear if this applies to initial screening or to evaluation of identified uses.³⁵⁰

For both compendia, there is significant room for interpretation of what is reviewed and what weight is assigned to any reviewed information. Both Lexi-Drugs and Gold Standard identify uses by monitoring CPGs.³⁵¹ But, as noted above, CPGs vary widely. There are over 3,700 CPGs and not all of them conform to the IOM’s recommendations.³⁵² How do compendia evaluate them? Are some weighted more than others? Lexi-Drugs also monitors “list servs” (i.e., email groups).³⁵³ Which ones? Who is on them? Do they screen the individuals on the list serv before initiating a request based on a member’s email or suggestion? Gold Standard looks at published literature,³⁵⁴ but does it also look at unpublished literature in ClincialTrials.gov? What kind of practitioner “interaction” does it have? How is that structured?

Here, then, is a place where compendia would benefit from more objective criteria and a standardized algorithm. As one example, consider the American Academy of Family CPG Manual, which includes relevance to the practice area and lack of evidence-based guidelines.³⁵⁵ Its approach draws on existing research exploring how to construct evidence-based CPGs.³⁵⁶

While these criteria are not especially meaty, they have more flesh than existing compendia practices. And they are quite easy to bulk up. In doing so, the agencies could address specific areas of concern—like conflicts of interest—that filter into various aspects of the review process. The agencies, for instance, could employ a tiered process that evaluates requests based on the identification of the requestor. Part of this approach might mean restricting the ability of pharmaceutical companies (or organizations or individuals they fund) to make

³⁴⁹ Lexi-Drugs Revision Request, *supra* note 226, at 7

³⁵⁰ *Id.*

³⁵¹ Clinical Pharmacology Revision Request, *supra* note 213; Lexi-Drugs Revision Request, *supra* note 226, at 7.

³⁵² IOM REPORT, *supra* note 75, at 2.

³⁵³ Lexi-Drugs Revision Request, *supra* note 226, at 7.

³⁵⁴ Clinical Pharmacology Revision Request, *supra* note 213.

³⁵⁵ See generally *Clinical Practice Guidelines Manual*, AAFP, <https://www.aafp.org/family-physician/patient-care/clinical-recommendations/cpg-manual.html#i> (last visited Oct. 14, 2020).

³⁵⁶ As noted above, the AHRQ used to work with organizations to develop guidelines but no longer does so. It developed nineteen such guidelines over a four-year period. *Clinical Practice Guidelines Archive*, AGENCY FOR HEALTHCARE RSCH. & QUALITY, <https://www.ahrq.gov/prevention/guidelines/archive.html> (last visited Oct. 14, 2020).

addition requests,³⁵⁷ or treating those requests with an extra layer of scrutiny. It might also mean requiring requesters to disclose any potential conflicts for their request to even be considered.

Another crucial checkpoint for standardization is the evaluative process. Just as compendia have no standardized process for identifying new uses, they have no similar process for evaluating the evidence they find. They do, of course, have processes for how they evaluate evidence.³⁵⁸ And they are not simply making subjective judgments. But these processes vary considerably by compendium and, as the 2009 MEDCAC study found, leave ample room for subjective assessment. Standardizing the process of identification and evaluation by a clear and detailed algorithm would increase reliability of compendia by decreasing the role of subjective assessment.

While a standardized process for evidence evaluation would increase reliability, it would not necessarily generate less variability. To reduce variability, the agencies should standardize and unify compendia's various evidence rating systems. Currently each compendium employs its own evidentiary rating system. Ratings in Lexi-Drugs do not correspond to ratings in DrugDex or any other compendium. Not only is this duplicative and wasteful, but it also makes it difficult for CMS to "cross-walk" ratings from one compendium to another.

To decrease this variability, the agencies could create a uniform rating scale and form that every compendium must use. This could be similar to the process that has been used effectively to develop CPGs.³⁵⁹ Each evidentiary grade, confidence level, and recommendation would appear on the same form and in the same format in each compendium. Uniform presentation would significantly reduce variability. Coupled with a standardized process for rating evidence, it might also increase reliability. The FDA could also require drug companies to append the form—an example of which is included in the Appendix ("FDA Form D-1")—as a cover page on all off-label communications. Doing so would provide physicians reliable, actionable information in a constitutional manner.

Each of these reforms should also be accompanied by an expanded disclosure requirement. By making all compendia processes and evaluation

³⁵⁷ This may raise First Amendment questions, some of which may implicate existing guidance documents. See FDA GUIDANCE: UNSOLICITED REQUESTS, *supra* note 59, at 4.

³⁵⁸ Compare Lexi-Drugs Revision Request, *supra* note 226, at 7–8, with Clinical Pharmacology Revision Request, *supra* note 213, and Elsevier Editorial Policy, *supra* note 258.

³⁵⁹ See *supra* Section I.A.2.

procedures public, compendia can enhance trustworthiness. Interested parties can learn about how compendia evaluate information and decide the compendia's reliability. Transparency will also allow public study; this is important not just for further government regulation, but also for interested parties, such as private insurance companies and pharmacy benefit managers, who rely on compendia for reimbursement and decision-making.

Two final regulatory backstops could also help ensure that compendia, once recognized, continue to maintain the same quality of information as when they applied for official status. One is a renewal requirement. Currently the CMS has not exercised its discretion to review existing compendia for compliance with its regulation; but it has removed one *sua sponte*.³⁶⁰ Given its broad authority, the CMS could require compendia to apply to renew their recognized status periodically (say, every five years). At each renewal, the CMS and the FDA could collaborate to review compendia to ensure that they comply with current regulatory standards.

A renewal requirement also represents an opportunity for the agencies to implement reforms as it continues to study compendia practices, reliability, and transparency. Although the CMS attempted to institute some additional reforms in 2009, it is unclear how much, if at all, these reforms changed compendia behavior because the CMS did not audit existing compendia to determine compliance with them. A renewal requirement would enable the CMS to ensure that compendia implement any additional changes to regulation.

Regardless of whether the CMS requires compendia to renew their recognized status, it could also audit or inspect them to ensure compliance with existing regulations. Audits could mirror the 2007 and 2009 studies of compendia, discussed above.³⁶¹ Or they could more closely resemble the FDA's inspections of drug manufacturers to ensure compliance with "good manufacturing practice."³⁶² Under the latter approach, for example, manufacturers are required to maintain various records and reports, as well as laboratory, production, and process controls, which include quality checks and testing.³⁶³ Similar requirements, adapted to the setting of drug evaluation, could be imposed on compendia. The two methods—a renewal requirement and

³⁶⁰ See *supra* Sections II.B, II.C.

³⁶¹ See *supra* Section II.D.

³⁶² 21 C.F.R. § 211.1 (2021).

³⁶³ E.g., 21 C.F.R. §§ 211.180–98 (2021) ("Records and Reports"); *id.* § 211.63 ("Equipment"); *id.* §§ 211.80–94 ("Control of Components and Drug Product Containers and Closures"); *id.* §§ 211.160–76 ("Laboratory Controls").

audits/inspections—are not mutually exclusive. But how the CMS and the FDA decide to regulate compendia may influence the method they use to ensure compliance.

These are simply suggestions. They point to a larger project that would require additional study—a prime opportunity for the CMS and the FDA to work collaboratively. Much like the IOM did in 2008 and 2011, the FDA and the CMS will need to engage in a detailed study and involve numerous stakeholders.³⁶⁴ The process will not be quick. The latest IOM report on CPGs spanned 266 pages and involved multiple stakeholders, experts, and government actors.³⁶⁵ But the result was a standard for better evidence-based CPGs.

A joint FDA-CMS study, however, has a leg up on the process of reforming compendia through more direct regulation. It can build on the previous work of both the IOM (CPGs) and the CMS (compendia) to develop a standardized process for identification, evaluation, and publication of the evidence for off-label uses in compendia. But it will still take initiative, collaboration, and cooperation of federal agencies, drug compendia, and stakeholders.

If this collaboration is successful, it will result in a double benefit. For the CMS, it means reimbursement decisions will be based on more reliable and less variable evaluations of evidence. This will reduce costs and improve care. For the FDA, it means the ability to administer a finely tuned regulatory regime for information about off-label uses. In this regime, the FDA can regulate off-label information based on the evidence supporting the use. This will further, rather than impair, what it claims are the two most important goals that off-label promotion undermines: patient cost and information production. It will, in other words, lead to evidence-based regulation of off-label information.

C. Illustrating Indirect Regulation

To make things concrete, this section provides three examples of how this new system might function. The first example uses the FDA Guidance to show how a compendia-based system that limits information activities based on the evidence supporting the relevant off-label use can apply to the existing FDA policy on off-label information dissemination. The second illustration shows

³⁶⁴ IOM REPORT, *supra* note 75, at 35–36; INST. OF MED., KNOWING WHAT WORKS IN HEALTH CARE: A ROADMAP FOR THE NATION 74–75 (Jill Eden, Ben Wheatley, Barbara McNeil & Harold Sox eds., 2008); *see also* INST. OF MED., CONFLICT OF INTEREST IN MEDICAL RESEARCH, EDUCATION, AND PRACTICE 58 (Bernard Lo & Marilyn J. Field eds., 2009).

³⁶⁵ *See generally* IOM REPORT, *supra* note 75.

that regulations can be toggled to increase or decrease information flows for drugs the FDA deems fill a significant need. The final example proposes funding generic manufacturers to engage in off-label information dissemination where generic, off-label drugs are more cost-effective than higher-cost (on- or off-label) ones. Both examples assume direct regulation of the type described above to make compendia a reliable source of off-label information.

1. Using the FDA Guidance Documents

Drafting an entire set of information regulations based on proposed, hypothetical changes to compendia cannot be done here. But to preview what regulations might look like, this section briefly sketches this Article's proposal by applying it to the existing FDA Guidance. Using the Guidance to illustrate this approach offers some key analytical advantages, despite its obvious shortcomings.³⁶⁶ First, it is a concrete framework with various choices about form, content, and dissemination that can be altered. Second, the framework is simple. Because it defines the set of permissible activities narrowly, changes to the framework are easily understandable. Third, it represents the current thinking of the FDA on off-label informational activities. Any proposal that seeks to change how the FDA regulates off-label information ought to show how the proposal would change or adapt existing FDA policy. Modifying the existing FDA framework demonstrates that this proposal could be integrated into existing FDA policy.

For the purposes of this exercise, assume that there are three off-label uses listed in one recognized compendium. To maintain simplicity, assume further that the compendium has a single rating scale, where it assigns grades of "A," "B," and "C," that correspond to the quality of the evidence and the recommendation of whether to prescribe it.

To tie information dissemination to evidence, the FDA could simply alter its Guidance based on the grade the use receives. An "A" grade, for example, might entitle the manufacturer to append to its communication the most supportive study for the use. Or it may be able to include excerpts of articles or highlighted

³⁶⁶ The most obvious shortcoming is that using the FDA's existing framework accepts the FDA's framing of the relevant issues. A second, related drawback is that there is a tightly constrained universe of permissible activities to alter. Finally, using the FDA Guidance also does not completely address the problems of vagueness described in Section I.B. Each of these problems is significant. And they, along with this section's analysis, illustrate that using the FDA's existing framework is likely to replicate many of its flaws. Because of this, the FDA Guidance should not be used as a baseline to craft new regulations. To understand the appropriate nature and scope of regulations, the HHS should commission a study and report on how to craft these rules under the new compendia-based system.

text from the articles supporting the use. The FDA might also refrain from imposing a requirement that all supportive reference texts must be in their complete, unabridged form. Finally, the regulations might allow distribution of any CPGs published by the compendia, and any other CPG that recommended the use in a manner consistent with the grade.

A use that receives a “B” rating, by contrast, would provide the manufacturer with less freedom than an “A” rating, but still more than provided by the Guidelines. They might, for example, allow excerpts from articles but not allow highlighting. They might also not require complete reference text chapters but require a bibliography of all references used by the compendia, organized by how strongly they support or conflict with the evidence in the compendia. Manufacturers also might be able to distribute only those CPGs published by a recognized compendium unless compendia do not publish any CPGs covering the use. In the latter case, additional requirements for CPGs could be imposed, including a requirement that the manufacturer distribute more than one CPG, each consistent with the grade assigned by the compendium.³⁶⁷

Uses that receive a “C” rating would be subject to the existing FDA Guidance. They would not, however, be allowed to distribute any CPGs. Existing rating systems typically list the lowest-rated use as “[n]ot recommended”³⁶⁸ and, hence, it would make little sense to allow drug manufacturers to distribute CPGs covering a use the compendia rated as not supported by the evidence.³⁶⁹

Regardless of how this graded system works—whether it functions as described or in some totally new manner—there is at least one other way that this proposal enables the FDA to combat the influence of pharmaceutical companies, open informational flows to physicians, and act within the

³⁶⁷ Some compendia include relevant CPGs, but it is not entirely clear how they decide to do so. As part of this project, I subscribed to Lexi-Drugs via its iOS application. In the entry for amantadine, Lexi-Drugs has various headings, including “Clinical Practice Guidelines.” Here, it lists only three CPGs for Parkinson’s and one for Schizophrenia and Antipsychotic Adverse Effects. American Academy of Neurology, “Treatment of Parkinson disease with motor fluctuations and dyskinesias,” April 2006; Canadian Neurological Sciences Federation, “Canadian Guidelines on Parkinson’s Disease,” 2012; National Institute for Health and Care Excellence, “Parkinson’s disease in adults,” 2017; World Federation of Societies of Biological Psychiatry, “Guidelines for the Biological Treatment of Schizophrenia, Part 2: Update 2012 on the Long-Term Treatment of Schizophrenia and Management of Antipsychotic-Induced Side Effects,” 2013 (citation based on personal review of author).

³⁶⁸ *E.g.*, Clinical Pharmacology Revision Request, *supra* note 213.

³⁶⁹ This proposal is not ideal, however, because it mimics a problem already caused by the existing FDA Guidance: an inability to specify *ex ante* which CPGs can be distributed. One way to avoid this problem is to require compendia to rate CPGs in addition to off-label uses.

constitutional limits set by recent court decisions: mandate any off-label communication use an FDA-approved disclosure form for each off-label use communicated. Although the current Guidance specifies certain form, content, and dissemination requirements, it does not mandate that manufacturers present information in a uniform format—or even in a format that is designed to inform physicians of the most relevant information, in the most appropriate order, or in the most concise manner possible. And it is not clear that the limits the FDA has set make an appreciable difference on physician prescribing behavior. This is a significant missed opportunity to influence provider interaction with off-label information.

A simple disclosure form, such as the FDA Form D-1 in the Appendix, could provide the most important information for physician decision-making, and also reflect the evidence supporting the disseminated off-label use. Providers looking at this form will quickly understand the difference between the on- and off-label uses and evidence supporting the disseminated off-label use. This form will serve as an important informational anchor for any physician evaluating the information contained in the communication.

It will also be constitutional. Under the First Amendment, disclaimers and additional information are often favored over information restriction. In *Caronia*, for example, the court stated that instead of banning off-label promotion, the “government could develop its warning or disclaimer systems, or develop safety tiers within the off-label market, to distinguish between drugs.”³⁷⁰ It stands to reason, then, that a simple disclosure form accompanying every manufacturer’s communication about an off-label use would be constitutional. It would also provide more useful information to the physician than requiring, as the current Guidelines do, the manufacturer to state that the use is not approved and to include a copy of the approved drug label.

The FDA Form D-1, like the application of my proposal described above, is an illustration.³⁷¹ Further research may reveal that an effective form presents

³⁷⁰ *United States v. Caronia*, 703 F.3d 149, 168 (2d Cir. 2012).

³⁷¹ This Article does not comment, for instance, on whether the disclosure form ought to be required or merely suggested. The former might raise the specter of a new First Amendment challenge the latter could avoid. Much would turn on the characterization of the disclosure document. If it concerns “purely factual and uncontroversial information about the terms under which . . . services will be available,” then the form should be upheld unless “unjustified or unduly burdensome.” *Zauderer v. Off. of Disciplinary Couns. of Sup. Ct. of Ohio*, 471 U.S. 626, 651 (1985). The FDA would have good grounds to argue that disclosure form protected the *listener’s* interest (doctors and by proxy patients) in freedom from deception. *Id.* (“[A]n advertiser’s rights are adequately protected as long as disclosure requirements are reasonably related to the State’s interest in preventing deception of consumers.”).

information in a different format or order—or perhaps even requires additional or different information. As an example, however, the FDA Form D-1 provides a template for thinking about how to structure physician interaction with off-label information in a concise, useful, and unbiased format.

2. *Toggling Informational/Promotional Activities*

Tinkering with FDA Guidance has obvious limitations. The changes are small, use an extant suboptimal framework, and may not produce a significant effect on either industry or physicians. While true, the point of the example was only that this new approach is compatible with the existing regulatory regime. In this section, however, this Article briefly sketches several *new* modes of regulation that do significantly vary from the existing framework and which are likely to have a significant effect on the use of off-label drugs.

Consider first an off-label use for an under-researched condition (or even an under-researched off-label use). To improve access to medications, for example, FDA regulations might permit increased informational activities for off-label uses that treat rare diseases on thinner evidence than it usually requires for other off-label uses.³⁷² These might include distributing limited promotional materials to physicians with or without Form D-1. Depending on both the need and the evidence base, the FDA could allow some limited (and different) direct marketing to patients, perhaps with a different set of advertising regulations.

Or the FDA may wish to increase prescriptions for safer off-label uses relative to unsafe ones. Since off-label uses of drugs that have been on the market the longest are those with the fewest adverse events,³⁷³ the FDA might loosen

It is also possible, however, that the current Supreme Court could find the information was neither “purely factual” nor “uncontroversial” (or both), in which case the reasoning above would not apply. *E.g.*, *Nat’l Inst. of Fam. & Life Advocs. v. Becerra*, 138 S. Ct. 2361, 2372 (2018) (holding that a state law requiring unlicensed anti-abortion centers to disclose their unlicensed status concerned a speech that was about “anything but an ‘uncontroversial’ topic”). If so, the disclosure document would be analyzed under the strict scrutiny framework. *Id.* at 2374–75. While these issues are complex and deserve analysis, they speak to implementation issues that go beyond the scope of this Article. For example, even if strict scrutiny applied, the FDA could avoid confronting the issue head on by issuing guidance documents recommending the use of the form. These issues, and others like them, are not addressed here.

³⁷² See Liang & Mackey, *supra* note 15, at 37–43. At the same time, it is possible to structure advertising rules can automatically tighten when certain benchmarks are met—say, a certain number of prescriptions have been written or a certain amount of data have been collected on an orphan use.

³⁷³ See Simon, *supra* note 5, at 723 & n.88; Tewodros Eguale, David L. Buckeridge, Aman Verma, Nancy E. Winslade, Andrea Benedetti, James A. Hanley & Robyn Tamblyn, *Association of Off-Label Drug Use and Adverse Drug Events in an Adult Population*, 176 JAMA INTERNAL MED. 55, 59 (2016) (“Drugs approved after 1995 had ADE rates that were 55% higher than drugs approved before 1981 (AHR, 1.55; 95% CI, 1.39–1.73), and the same is true for drugs approved from 1981 to 1995 (AHR, 1.62; 95% CI, 1.45–1.80).” (citation omitted)).

promotional restrictions—or pay companies to disseminate information—for off-label uses of (some) generic drugs that meet certain evidentiary thresholds (discussed more in Section III.C.3).³⁷⁴ If generic manufacturers can disseminate information about or promote their off-label uses with greater freedom—or if they (or third-party companies) are paid to do so—the FDA’s policy might also save consumers money by stimulating physicians to prescribe more cost-effective treatments.³⁷⁵

These are simple proposals meant to illustrate the flexibility this regulatory regime; many others are conceivable. Whatever new modes of regulation the FDA chooses, it can preserve traditional incentives for drug research and development, including new indications.³⁷⁶ Graded regulations make strongly supported off-label uses much more attractive than poorly supported ones, but also much less attractive than on-label advertising generally. And since virtually no sNDAs are filed for drugs lacking patent protection or regulatory exclusivity, one way the FDA could preserve incentives for sNDA filing is to loosen promotional restrictions only as to these “unprotected” drugs (provided they met a predetermined evidentiary threshold).³⁷⁷ In some cases, the FDA might consider loosening promotional restrictions even for “protected” drugs where

³⁷⁴ This is different from the traditional approaches to combatting detailing of high-margin, high-profit drugs, which can be done using at least two different “counter-detailing” tools. One academic detailing entails education programs designed to reduce costs by providing physicians with better information about drugs. See *infra* Section III.C.3. The other involves requiring detailers to present alternative treatment options. *E.g.*, Sorrell v. IMS Health Inc., 564 U.S. 552, 560 (2011) (noting that the statute at issue, as originally enacted, “required detailers to provide information about alternative treatment options,” which was later repealed); Declaration of Jerry Avorn & Aaron S. Kesselheim at 1–6, IMS Health Inc. v. Ayotte, 490 F. Supp. 2d 163 (D.N.H. 2007), *rev’d and vacated*, 550 F.3d 42 (1st Cir. 2008) (No. 06-cv-280) [hereinafter Avorn & Kesselheim Declaration] (explaining academic detailing, its purpose, and its success). Given the Supreme Court’s jurisprudence, it is hard to see the latter kind of regulation surviving First Amendment scrutiny. Traditionally, academic detailing has focused on how to combat the tendency to prescribe expensive on-label drugs over inexpensive on-label ones. See Avorn & Kesselheim Declaration, *supra*, at 10–11. The approach this Article advocates here is to fund generic manufacturers or their associations to provide information about *off-label uses of generics* that have therapeutic value. This Article explains this in greater detail in this section.

³⁷⁵ Generics could do this either by using existing partnerships or forming new ones to undertake advertising for off-label uses of generic drugs. One such organization for generic lobbying has rebranded to become the Association for Accessible Medicines. See *About the Association*, ASS’N FOR ACCESSIBLE MEDS., <https://accessiblemeds.org/about> (last visited Oct. 14, 2020); Association for Accessible Medicines (AAM), *Generic Pharmaceutical Association Becomes Association for Accessible Medicines*, PHARM. PROCESSING WORLD (Feb. 14, 2017), <https://www.pharmaceuticalprocessingworld.com/generic-pharmaceutical-association-becomes-association-for-accessible-medicines/>.

³⁷⁶ Given that there are limited data about what drives firms to file sNDAs, it is not possible presently to specify what this regulatory regime looks like. It is also true that many off-label uses will never be brought on-label.

³⁷⁷ See Sahragardjoonegani et al., *supra* note 170, at 2; Benjamin Berger, Amitabh Chandra & Craig Garthwaite, *Regulatory Approval and Expanded Market Size* 9 & n. 29 (Nat’l Bureau of Econ. Rsch., Working Paper no. 28889, 2021), <https://www.nber.org/papers/w28889>.

the evidence supporting the use is strong. The FDA could also limit the time period for promotion, require the drug manufacturer to collect additional post-market information on the drug, and potentially even open a pathway for approval of the new indication based on this information.³⁷⁸ A properly structured graded regulatory regime, in other words, can encourage accumulation and disclosure of evidence about off-label uses without destabilizing incentives to conduct clinical trials necessary to bring some off-label uses on-label.

3. *Off-Label Detailing*

A regulated, compendia-based rating system also opens an alternative mechanism to counteract the tendency of manufacturers to provide information about higher-cost off-label uses instead of lower-cost ones: disseminate, or pay others to disseminate, information about cost-effective generic off-label alternatives, or what this Article calls “off-label detailing.” The concept is not new. Something similar—a practice known as “academic detailing”—has been done effectively in the context of drug advertising for several decades. Academic detailing involves evaluating therapies, training clinicians on drug education, and using these trained physicians to “detail” other physicians and educate them on the most cost-effective therapeutic choices.³⁷⁹ Physicians educated in this way tend to make more cost-effective choices for their patients, driving down drug costs.³⁸⁰

A similar approach could be used in the context of off-label prescribing, particularly where there are effective off-label uses that are cheaper than on-label ones, or where there are two equally supported off-label uses that differ significantly in price.³⁸¹ Unlike traditional academic detailing, which includes systematic review and evaluation of evidence, off-label detailing would be less expensive because, in the system this Article has proposed, compendia already evaluate the evidence supporting off-label uses. The FDA or the CMS would, of course, still need to decide which off-label uses are cost-effective alternatives, but compendia would have completed a large portion of that work for them. The

³⁷⁸ See generally 21 U.S.C. § 355f (explaining current regulations). The FDA has already begun promoting the integration of clinical trials into practice settings. U.S. FOOD & DRUG ADMIN., FRAMEWORK FOR FDA’S REAL-WORLD EVIDENCE PROGRAM 10–11 (2018).

³⁷⁹ For a brief review of academic detailing and its history, see generally Jerry Avorn, *Academic Detailing: “Marketing” the Best Evidence to Clinicians*, 317 JAMA 361 (2017).

³⁸⁰ *Id.*

³⁸¹ Drug pricing and reimbursement is complicated and varies by payor. See generally ROBIN FELDMAN, DRUGS, MONEY, AND SECRET HANDSHAKES (2019).

FDA's (or the CMS's) main task would be to decide *how* to disseminate the information—either by creating an exception to its ban on “promotion” or by increasing the kinds of information that can be distributed about them. Beyond those decisions, however, training personnel and using them to disseminate information, or paying others to disseminate it, would be the principal costs.

Assume, for example, that there is currently an on-label, expensive drug for condition X and an off-label, generic drug that has roughly the same efficacy for the same condition. To stick with the rating system in the previous section, imagine the recognized compendia all rate as “A” the off-label use. In this case, the FDA would take two steps to implement off-label detailing. The first is to expand the kind and nature of permissible information-related activities, potentially lifting or modifying the ban on promotion. Second, either the FDA or the CMS would fund these activities by training their own personnel or contracting with third parties, including academics, medical centers, and even (associations of) generic manufacturers.³⁸²

Off-label detailing could effectively curb drug costs and curtail unnecessary off-label prescriptions. Physicians would be most likely to learn about cheap, effective off-label uses and less likely to learn about less-effective off-label uses. Why? Because the FDA, the CMS, or third parties would actively promote the most effective therapies, and the FDA regulations and Form D-1 would limit the amount and nature of information physicians would receive about less effective off-label uses. The result: doctors would prescribe more effective, less expensive off-label uses more often than less effective, more expensive ones.

CONCLUSION

This Article has articulated a new framework to regulate information about off-label uses. It argued that the FDA's current policy suffers from legal and practical challenges—challenges that can be overcome by developing a more flexible and nuanced approach to off-label information that tied regulation directly to evidence. To accomplish this, this Article argued that the FDA should more closely regulate and rely on drug compendia: private entities that organize, evaluate, and grade evidence supporting off-label uses. Uses supported by more evidence (i.e., those rated highly by compendia) would face fewer informational restrictions than those supported by less or no evidence (i.e., those rated poorly

³⁸² Currently, generic manufacturers' margins are so thin that they fail to engage in much, if any, off-label communications or advertising more generally. Here, using generic manufacturers may be the most effective option because they are likely to have the greatest incentive to increase the use of their product without incurring any costs to do so. This would, of course, also raise questions of influence that the regulations try to combat.

by compendia). After explaining how to achieve this aim, this Article provided three examples of how this system might work. They showed not only that this regime is workable, but that it is compatible with the existing FDA framework and, crucially, constitutional.

APPENDIX

FDA Form D-1**1. DRUG & APPROVED USE**

Drug (brand name):	[drug(brand)]
Approved Uses:	<i>Indications & Usage:</i> [indications & usage]
	<i>Dosage & Administration:</i> [dosage & administration]
	<i>Warnings:</i> [warnings]

2. DISSEMINATED OFF-LABEL USE

Off-Label Use Disclosed:	<i>Indications & Usage:</i> [indications & usage]
	<i>Dosage & Administration:</i> [dosage & administration]
	<i>Warnings:</i> [warnings]

3. RATING & RECOMMENDATIONS FOR OFF-LABEL USE

Evidentiary Grade Supporting the Disclosed Off-Label Use, by Compendia:	Grade	Compendium
	[grade]	[compendium]

Average Total Grade:

[Average Total Grade]

Explanation of Ratings:

A – [explanation]
B – [explanation]
C – [explanation]
D – [explanation]

Recommendation:

Recommendation	Compendium
[recommendation]	[compendium]

Recommendation³⁸³

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Explanation of Recommendations

Recommended – [explanation]
Equivocal - [explanation]
Not recommended – [explanation]

4. REFERENCES

Support, by	Study Type	# of Studies	Positive / Negative / Neutral	
Study Type ³⁸⁴	Meta-analysis	[n]	[n \oplus /n \ominus /n \circ]	
	Phase IV <i>Randomized 2-arm</i> <i>Single-arm</i>			
	Phase III <i>Randomized 2-arm</i> <i>Single-arm</i>			
	Phase II <i>Randomized 2-arm</i> <i>Single-arm</i>			
	Phase I			
	Phase 0			
	Observational			
	Case Series			
	Trial of N=1			
	Case Report			
	Preclinical			
	Total		[n]	[n \oplus /n \ominus /n \circ]

³⁸³ The “recommendation” field would occur in singular form only on this form when used by compendia.

³⁸⁴ This chart could also be represented as a graph on a separate page or in lieu of the table.