

Off-Label Drug Risks: Toward a New FDA Regulatory Approach

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Abstract

Most off-label uses of prescription drugs are not supported by strong clinical evidence, leading to millions of patients being exposed to poorly understood risks without well-established benefits. The FDA's approach to limiting these risks has been to bar manufacturers from promoting their drugs for off-label uses. But this strategy has had only limited success and is threatened by courts' increasing willingness to extend First Amendment protections to drug makers' speech. This Article proposes that the FDA should shift its focus from off-label promotion toward off-label prescribing. The Agency should provide information on drug labels about the strength of the evidence that supports common off-label drug uses. Leveraging the FDA's unique ability to gather and analyze information and physicians' role as learned intermediaries could alter prescriber practices to reduce the rate of unsupported off-label drug uses.

Introduction

Well over a million people in the United States are injured or killed by prescription drugs each year.¹ The challenge for regulators is to ensure that drugs are safe and effective² while limiting the adverse effects of regulation on innovation and timely access to new products.³ In the United States the primary regulator of drug safety is the federal Food and Drug Administrator (FDA).⁴ Before a manufacturer can market a prescription drug it must obtain FDA approval

¹ See Justin M. Mann, *FDA Adverse Event Reporting System: Recruiting Doctors to Make Surveillance a Little Less Passive*, 70 FOOD & DRUG L.J. 371, 381 (2015) (citing 2013 data that 1.1 million voluntary reports of injuries and death were submitted to the FDA's Adverse Event Reporting System [FAERS]).

² See Pure Food and Drug Act, Pub. L. No. 59-384, § 2, 34 Stat. 768, 768 (1906) (repealed) (prohibiting sale of "misbranded or adulterated or poisonous or deleterious . . . drugs [and] medicines"); see also Federal Food, Drug, and Cosmetic Act, Pub. L. No. 75-717, 52 Stat. 1040, 1040 (1938) (to be codified as amended at 21 U.S.C. §§ 301 et seq.) (prohibiting interstate movement of misbranded and adulterated drugs and devices); Keefauver-Harris Amendments of 1962, Pub. L. No. 87-781, § 102, 76 Stat. 780, 780 (1962) ("An act to protect the public health."); *id.* (adding effectiveness as criterion for new drug approval).

³ See Drug Price Competition and Patent Term Restoration Act of 1984, 21 U.S.C. § 355 (j)(2)(18), Pub. L. No. 98-417, 98 Stat. 1585 (1984) (creating streamlined Abbreviated New Drug Approval pathway for generic drugs); see also Food & Drug Administration Modernization Act of 1997, Pub. L. No. 105-115, 111 Stat. 2296 (1997) (establishing the least burdensome principle for ensuring medical device effectiveness and substantial equivalence); see also 21st Century Cures Act, Pub. L. No. 114-255, 130 Stat. 1033 (2016) (strengthening and extending application of burdensome principle).

⁴ See Richard A. Merrill, *The Architecture of Government Regulation of Medical Products*, 82 VA. L. REV. 1753, 1764 (1996) (describing FDA's role as overseeing a system of comprehensive drug licensure).

through either the New Drug Application (NDA) process (for “new” or brand drugs) or the Abbreviated NDA (ANDA) process (for generic drugs).⁵ These processes provide the FDA with a wealth of information about drug safety and effectiveness.⁶

The primary way through which the FDA communicates this information about drug risk and effectiveness to prescribers is through the drug label, which the Agency describes as a “compilation of information based on a thorough analysis of the new drug application.”⁷ The information presented in a label “must be based whenever possible on data derived from human experience,”⁸ and must be limited to the indications for which the drug has been approved.⁹ Information about non-approved (off-label) uses generally may not be included on a drug label.¹⁰

Off-label drug use is a necessary and proper part of medical practice.¹¹ Overall, an estimated twenty-one to fifty percent of all prescriptions are for off-label indications.¹² In some patient groups, this number may exceed eighty percent.¹³ Many of these uses have become the standard of care.¹⁴ On the other hand, many off-label uses—up to seventy-nine percent by some

⁵ See 21 U.S.C. §§ 355(b), (j) (2018) (establishing the new drug application process for new drugs in subsection (b) and the abbreviated new drug application for the bioequivalent, generic, version of a previously approved drug in subsection (j)).

⁶ *Id.*

⁷ See Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products, 71 Fed. Reg. 3922, 3968 (Jan. 24, 2006) (citing the FDA’s preamble in its 2000 proposed rules amending the 1979 physician labeling regulations); See 21 C.F.R. § 1.3(a), (b) (2019) (“Labeling” is a broader category of materials than “label.” The FDA defines the latter as “any display of written, printed, or graphic matter on the immediate container of any article.” Labeling “includes all written, printed, or graphic matter accompanying an article at any time while such article is in interstate commerce or held for sale after shipment or delivery in interstate commerce.”).

⁸ 21 C.F.R. § 201.56(a)(3) (2019).

⁹ See 21 C.F.R. §201.57(c)(2) (2019) (discussing that the label must state that the drug is indicated for use in connection with specific diseases or conditions).

¹⁰ See *infra* Part II (describing FDA’s regulation of off-label promotion).

¹¹ See Christian Tomaszewski, *Off-Label: Just What the Doctor Ordered*, 2 J. MED. TOXICOLOGY 87, 87 (2006) (citing the holding from *Buckman Co. v. Plaintiff’s Legal Comm.* - “The U.S. Supreme Court has ruled that the ‘off-label usage of medical devices is an accepted and necessary corollary of the FDA’s mission to regulate. . . .”).

¹² Aaron S. Kesselheim, *Off-Label Drug Use and Promotion: Balancing Public Health Goals and Commercial Speech*, 37 AM. J.L. & MED. 225, 234 (2011).

¹³ See generally, Nathan Cortez, *The Statutory Case Against Off-Label Promotion*, 83 U. CHI. L. REV. 124, 125 (2017) (“Off-label uses can even constitute the standard of care in disciplines like oncology, neurology, and psychiatry.”).

¹⁴ See Tomaszewski, *supra* note 11, at 87 (describing the off-label uses of intravenous Mucomyst for acetaminophen overdose, octreotide for sulfonylurea overdose, and insulin infusion for verapamil overdose as “doing the right thing”).

estimates—are not supported by strong clinical evidence.¹⁵ As a result, physicians write millions of prescriptions each year for drugs that may be ineffective and risky for the conditions being treated.¹⁶

This Article seeks to accomplish two goals. One goal is to provide a framework for a new approach to reducing the risks associated with off-label drug use. Traditionally, the FDA has attempted to address the risks of off-label drug use by regulating manufacturers' off-label promotion,¹⁷ but these attempts have at best yielded only limited success.¹⁸ Manufacturers continue to promote their drugs for off-label indications and physicians continue to prescribe drugs for off-label indications, even in the absence of supporting evidence.¹⁹ In this Article, I propose a new way the FDA can address physicians' off-label prescribing practices.

The second goal is to help make drug labels more valuable to their intended audience, the physicians who prescribe drugs. My proposal involves a modification of drug labels that could succinctly provide physicians with information about how well supported, or unsupported, their off-label prescriptions are. The proposal builds upon recent studies by a collaboration of medical researchers that have identified a simple algorithm that facilitates the division off-label uses into those which are no more risky than FDA-approved uses from those which carry significantly higher risks.²⁰

This Article proceeds in four parts. Part I examines approved and off-label drug uses. After the thorough premarket evaluation of drug through the NDA or ANDA process, the risks

¹⁵ Cortez, *supra* note 14, at 125.

¹⁶ *See id.* (stating when a physician prescribes off-label, patients can be exposed to considerable risks).

¹⁷ *See* Michelle M. Mello et al., *Shifting Terrain in the Regulation of Off-Label Promotion of Pharmaceuticals*, 360 N. ENGL. J. MED. 1557, 1557 (2009) (“The agency has long maintained the general position that although physicians may freely prescribe drugs for off-label uses, drug manufacturers may not promote such uses.”).

¹⁸ *See infra* Part II.

¹⁹ Elizabeth Richardson, *Health Policy Brief: Off-Label Drug Promotion*, HEALTH AFFS. 1, 1-2 (June. 30, 2016).

²⁰ *See infra* Part I.B.

and benefits of the uses of that drug for approved indications are very well, albeit imperfectly, characterized. By contrast, the risks and benefits of the uses of that drug for off-label indications are often poorly characterized. But this obscures an important distinction: off-label uses that have strong supporting data are not riskier than on-label uses. By contrast, off-label uses that lack strong support are significantly riskier.

Part II examines the FDA's traditional approach to addressing the risks of off-label uses, the regulation of manufacturers' off-label promotion. As this Part shows, FDA's approach is flawed for several reasons. It may inhibit valuable information exchanges, has not prevented off-label promotion, and has been undermined by recent court decisions and legislative actions.²¹

Part III of this Article provides context for my proposal by reviewing some of the proposals that other scholars have put forward to address the risks associated with off-label drug use. Many scholars have focused on shoring up the FDA's existing ability to police off-label promotion. Others have proposed ways to expand the FDA's ability to regulate off-label promotion. This Part highlights a recent, ambitious proposal by Professors Ryan Abbott and Ian Ayres which suggested ways in which the FDA might influence physicians' off-label prescribing.

Part IV sets out my proposal. Rather than focusing on manufacturers' off-label promotion, this proposal focuses on providing information to prescribers about the available clinical data concerning the risks and benefits of off-label uses. Under the proposal, a duty to disclose is imposed on the drug's manufacturer once off-label prescriptions for a certain condition account for a certain volume or percentage of a drug's total prescriptions. The content of this duty is for the manufacturer to disclose to the FDA all clinical trials, experience, and

²¹ See *infra* Part II; see generally Mello et al., *supra* note 17, at 1558-61 (stating that the FDA has not prevented off-label promotion in a discussion of both past and present FDA regulation).

expert consensus statements that provide information on the risks and benefits of the drug’s off-label use of which the manufacturer knows or should know. The FDA would evaluate the quality of the data submitted but would not make a formal risk-benefit determination. Rather, the Agency would assign a “level of evidence” rating using an algorithm used by medical researchers. One possible implementation would yield a simple “Supported by Strong Evidence” or “Not Supported by Strong Evidence” binary rating, which could be incorporated into the first page of the FDA-approved drug label.

This proposal attempts to harness physicians’ status as learned intermediaries and their awareness of the threat of liability for negligence or malpractice. Providing physicians with information, especially information that an off-label use, no matter how widely accepted, is not supported by strong evidence should serve at a minimum as a stimulus for prescribers to evaluate the clinical data. This Part concludes with a preliminary discussion of some potential difficulties raised by the proposal.

I. Off-Label Drug Use and the Information Deficit Problem

Over the course of the twentieth century, mortality rates in the United States declined by an astounding fifty percent,²² and life expectancy at birth increased by an equally astounding twenty-nine years.²³ While broad public health measures such as improved sanitation, reduced smoking rates, and improved nutrition drove much of this improvement, prescription drugs were also key contributors.²⁴ However, over a million people in the United States are injured or killed

²² See U.S. CENSUS BUREAU, STATISTICAL ABSTRACT OF THE UNITED STATES: 1999 874 tbl.1420, <https://www.census.gov/prod/99pubs/99statab/sec31.pdf> (last visited October 12, 2019) (reporting a death rate per 1000 per year in 1900 of 17.2 and in 1997 of 8.6).

²³ *Id.* at 874, tbl.1421.

²⁴ See generally, David R. Francis, *Why Do Death Rates Decline?*, NAT’L BUREAU ECON. RES., <https://www.nber.org/digest/mar02/w8556.html> (discussing how the improvement in mortality rates is attributable to medical products and other changes that took place over the same period) (last visited Nov. 8, 2019).

by prescription drugs each year.²⁵ The challenge from a regulatory perspective is to ensure that drugs are safe and effective²⁶ while limiting the adverse effects that regulation may have on innovation and timely access to new products.²⁷

The FDA is the primary regulator of drug safety in the United States.²⁸ As the “gatekeeper” tasked with approving drugs before they may be marketed in the United States, the FDA gathers a vast amount of information about drug safety and effectiveness through the NDA and ANDA processes.²⁹ The chief way through which the FDA communicates information about drug risk and effectiveness to prescribers is through the drug label, which the Agency describes as the “compilation of information based on a thorough analysis of the new drug application”³⁰ FDA stated in a 2006 Final Rule that drug labels are “[t]he centerpiece for risk management of prescription drugs”³¹

FDA regulations establish that drug labels “must contain a summary of the essential scientific information needed for the safe and effective use of the drug.”³² The label “must be informative and accurate and neither promotional in tone nor false or misleading in any

²⁵ See Marcia Boumil, *FDA Approval of Drugs and Devices: Preemption of State Laws for Parallel Tort Claims*, 18 J. HEALTH CARE L. & POL’Y 1, 6 (2015), (citing estimates that over 100,000 people in the United States die from causes related to prescription drugs and medical devices); Mann, *supra* note 1, at 381 (citing 2013 data that 1.1 million voluntary reports of injuries and death were submitted to the FDA’s Adverse Event Reporting System (FAERS)); Thomas J. Moore, et al., *Serious Adverse Drug Events Reported to the Food and Drug Administration, 1998-2005*, 167 ARCH. INTERN. MED. 1752, 1754 (2007) (stating that one-sixth of the FAERS reports were for deaths due to prescription drugs).

²⁶ 529 U.S. at 133; § 102, 76 Stat. at 781 (adding effectiveness as criterion for new drug approval).

²⁷ See Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L.No. 98-417, 98 Stat. 1585 (creating Abbreviated New Drug Approval pathway for generic drugs); Food & Drug Administration Modernization Act of 1997, *supra* note 3, (establishing the least burdensome principle for ensuring medical device effectiveness and substantial equivalence); 21st Century Cures Act, Pub. L. No. 114-255, 130 Stat. 1033 (strengthening and extending application of burdensome principle).

²⁸ Merrill, *supra* note 4, at 1764.

²⁹ 21 U.S.C. § 355 (2018).

³⁰ Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products, 71 Fed. Reg. 3921, 3922 (Jan. 24, 2006).

³¹ *Id.*

³² 21 C.F.R. § 201.56(a)(1) (2019).

particular.”³³ The information provided in the label “must be based whenever possible on data derived from human experience.”³⁴ Other information—specifically data from animal studies—has a more restricted role.³⁵ “Conclusions based on animal data but necessary for safe and effective use of the drug in humans must be identified as such and included with human data in the appropriate section of the labeling.”³⁶ And crucial here, information about non-approved (off-label) uses is generally forbidden.³⁷

The FDA views drug labels as its principal tool for educating health care professionals about the risks and benefits of approved drugs.³⁸ A drug’s label is important to its manufacturer because it determines the bounds of the manufacturer’s promotional efforts.³⁹ The label is important to lawyers and courts, who scrutinize the contents of a drug’s label to assess whether the drug was negligently prescribed and whether the manufacturer satisfied its duty to warn.

So, drug labels are important to everyone. Everyone, that is, except to the one group toward whom they are actually directed: the health care providers who prescribe drugs. Physicians have a jaundiced view of drug labels that arises from concerns that the information on drug labels is written from a marketing perspective, and thus, exaggerate the potential benefits, and also from a liability avoidance perspective, and thus list even the most remote possible

³³ *Id.* § 201.56(a)(2).

³⁴ *Id.* § 201.56(a)(3).

³⁵ *Id.*

³⁶ *Id.*

³⁷ See *infra* Part II (discussing FDA’s regulation of off-label promotion and drug labels).

³⁸ See generally FDA CONSUMER HEALTH INFO, A GUIDE TO DRUG SAFETY TERMS AT FDA, at 2 (Nov. 2012), <https://www.fda.gov/media/74382/download>. (FDA stating the purpose of prescription drug labeling).

³⁹ Mello et al., *supra* note 17.

risks.⁴⁰ Physicians also worry that the information on drugs labels may be incomplete.⁴¹ Frequently, important information such as potential adverse effects and limitations on effectiveness for off-label uses are not contained on the label.⁴² As a result, studies have consistently shown that physicians are unaware of whether the FDA has approved the drugs they commonly prescribe for the indications they are treating: physicians often are unaware that they are prescribing drugs off-label.⁴³

This Part sets out the relevant issues surrounding the risks of off-label drug use and the information the FDA provides to physicians through drug labels. Part I.A examines uses of a drug for which the sponsor has sought and obtained FDA approval. The uses are associated with relatively small information deficits (compared to many off-label uses) regarding risk and effectiveness, although these deficits are still significant. Part I.B then examines the information deficits associated with off-label drug uses. Often these uses are supported by little empirical evidence. This has the potential to expose patients to harm without a reasonable anticipated benefit, but new findings by medical researchers permits a more granular assessment of the risk associated with off-label drug use. Thus, the discussion in Part I.B sets the stage for the remainder of this Article. Part I.C then examines how the FDA’s drug label regime fails to provide relevant information to prescribers.

⁴⁰ See Donna T. Chen et al., *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) (“Legal scholars note the primary purpose of FDA labeling is to guide industry marketing. As a result, many commentators assert that it is not labeling, but strength of clinical evidence, that physicians should be aware of and use to guide prescribing.”).

⁴¹ See Aaron S. Kesselheim & Jerry Avorn, Commentary, *The Role of Litigation in Defining Drug Risks*, 297 JAMA 308, 308 (2007) (“[A] drug’s label can vary in its completeness and balance and may not be updated in a timely way to reflect new data.”).

⁴² See *id.* (such information is often not presented on the label as “There are often important gaps in the ascertainment and reporting of adverse effects associated with prescription drugs . . . In both the premarketing and post marketing states, lawsuits have helped uncover important and previously unavailable data about major adverse events.”).

⁴³ See, e.g., Donna T. Chen et al., *supra* note 40, at 1098 (reporting study in which physicians correctly identified FDA-approved indications for commonly prescribed drugs just over half the time).

Before proceeding, I offer one brief note on terminology: The focus of this Article demands that I distinguish between drug promotion and prescribing. Thus, when discussing drug sponsor’s efforts to convince prescribers to prescribe their drugs, I use terms including “on-label promotion” and “off-label promotion.” In keeping with the FDA’s broad definition of drug promotion, I include under the term “promotion” activities such as sponsoring provider educational events and distributing reprints of scientific studies, in addition to traditional sales efforts such as advertising and detailing. When discussing physician and other providers’ prescribing of drugs, I will use terms including “on-label prescribing” and “off-label prescribing,” and “on-label use” and “off-label use.” And when discussing both off-label prescribing and promotion, I will use the term “off-label activities.”

A. Approved Drug Uses and the Drug Label

The medical products regulatory system utilizes four main sources of information about drug and device risk: information obtained simply by characterizing a product as a drug or device,⁴⁴ information generated through the FDA’s premarket evaluation processes,⁴⁵ information generated through post-market studies and adverse event reporting,⁴⁶ and information generated or disclosed through discovery and trial in failure-to-warn cases.⁴⁷ The limited understanding of the structure and function of discovered drugs and of human biochemistry make it nearly impossible to predict the existence of specific risks and to estimate

⁴⁴ JUDITH A. JOHNSON, CONG. RESEARCH OFFICE, FDA REGULATION OF MEDICAL DEVICES 5 (2016) (“Device classification determines the type of regulatory requirements that a manufacturer must follow.”).

⁴⁵ *See id.* at 9 (describing Premarket Approval Process requirement for sufficient scientific evidence to permit a reasonable assurance of safety).

⁴⁶ *See id.* at 30-31 (describing the primary objective of post market surveillance as gathering data on device failures and the device’s impact on the intended population.)

⁴⁷ *See generally id.* (discussing regulation of Medical Devices including characterizing a product, the pre-market and post-market process, and warning letters).

the magnitude of those risks.⁴⁸ Drug risks can be characterized only after large numbers of humans were exposed to new drugs.⁴⁹

Thus, there is a large information deficit regarding the risks posed by all new drugs at the beginning of their life cycle. The primary means by which the safety and effectiveness of prescription drugs are assured in the United States is the FDA's premarket evaluation process.⁵⁰ A manufacturer (or "sponsor") seeking to market a "new drug"⁵¹ must submit an NDA, which imposes the most rigorous information generating and disclosure requirements to which any FDA-regulated product is subjected.⁵² The sponsor must identify the specific condition or conditions for which it seeks FDA approval.⁵³ The sponsor must generate extensive amounts of new information about risk and effectiveness by conducting scientific studies, including at least two well-designed Phase 3 clinical trials.⁵⁴ The Phase 3 clinical trials "are intended to gather the additional information about effectiveness and safety that is needed to evaluate the overall

⁴⁸ See Dorothy Davies & Julian Davies, *Origins and Evolution of Antibiotic Resistance*, 74 MICROBIOL. MOL. BIOL. REV. 417, 417 (2010) (noting that successful treatments followed the discovery of antibiotics a half century after the late nineteenth-century discovery of certain infectious agents).

⁴⁹ See *The FDA's Drug Review Process: Ensuring Drugs Are Safe and Effective*, U.S. FOOD & DRUG ADMIN. (Nov. 24, 2017), <https://www.fda.gov/drugs/drug-information-consumers/fdas-drug-review-process-ensuring-drugs-are-safe-and-effective> (explaining that clinical trials for new drugs test approximately 3,000 subjects) [hereinafter FDA's Drug Review Process]. By contrast, the mid-twentieth century model of medical device development was one of product design rather than discovery. Because devices are designed, the site, nature and risks of their actions were viewed as predictable.

⁵⁰ 21 U.S.C. § 321 (2016).

⁵¹ *Id.* ("New drugs" are defined as drugs which are "not generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof" or which "[have] not, otherwise than in such investigations, been used to a material extent or for a material time under such conditions.").

⁵² 21 C.F.R. § 312.20 (1997); 21 C.F.R. § 312.23 (2002); FDA's Drug Review Process, *supra* note 49.

⁵³ 21 C.F.R. § 312.23 (2002).

⁵⁴ 21 C.F.R. § 312.21 (2002); (Before Phase 3 trials are conducted, a manufacturer must present preclinical data and conduct Phase 1 and 2 clinical trials. Phase 1 trials involve twenty to eighty individuals and "are designed to determine the metabolism and pharmacologic actions of the drug in humans, the side effects associated with increasing doses, and, if possible, to gain early evidence on effectiveness." Phase 2 trials include up to several hundred patients with the disease or condition for which the drug is to be marketed, and aim "to evaluate the effectiveness of the drug . . . and to determine the common short-term side effects and risks associated with the drug."); U.S. Food and Drug Admin., *Development & Approval Process (Drugs)*, U.S. FOOD & DRUG ADMIN. (Jan. 16, 2018), <https://www.fda.gov/Drugs/DevelopmentApprovalProcess/default.htm>.

benefit-risk relationship of the drug.”⁵⁵ Phase 3 trials are scientifically rigorous, employing the randomized assignment of subjects to active treatment and control arms, double-blinding of subjects and investigators, prespecified endpoints, and detailed statistical analysis.⁵⁶ These trials involve several thousand subjects and typically require several years to complete.⁵⁷

Manufacturers must also disclose extensive amounts of information, including pertinent animal data, known and potential adverse effects of the drug, clinically significant drug-drug interactions, and epidemiologic data on related drugs.⁵⁸ By the time a new drug completes its Phase 3 trials, the amount of information available to the FDA regarding its risks and effectiveness is larger than the information available for any other regulated product.

However, even Phase 3 clinical trials cannot identify all significant new drug risks. In fact, it is common for the NDA process not to detect adverse effects.⁵⁹ For example, for the 222 new drugs approved between 2001 and 2010, thirty-two percent had a post-market safety event.⁶⁰ The median time to a safety event was over four years after FDA approval.⁶¹

In contrast to the NDA process for new drugs, the Drug Price Competition and Patent Term Restoration Act of 1984 (Hatch-Waxman Act) established a relatively quick, low-cost

⁵⁵ 21 C.F.R. § 312.21 (2002).

⁵⁶ See Elena Losina et al., *OARSI Clinical Trials Recommendations: Key Analytic Considerations in Design, Analysis, and Reporting of Randomized Controlled Trials in Osteoarthritis*, 23 *OSTEOARTHRITIS & CARTILAGE*, 677, 678 (2015) (providing an example of the clinical trials for osteoarthritis treatment involving randomization, double-blinding and statistical analysis).

⁵⁷ U.S. Food and Drug Admin., *The Drug Development Process, Step 3: Clinical Research*, U.S. FOOD & DRUG ADMIN. (Oct. 14, 2016), <http://www.fda.gov/ForPatients/Approvals/Drugs/ucm405622.htm>.

⁵⁸ 21 C.F.R. § 314.50 (2008). This includes information generated by the sponsor as well as information from any other source. Manufacturers must also disclose the conditions prescribed, recommended, or suggested for the drug’s use, the methods used in, and the facilities and controls used for, the manufacture, processing, and packing, and the manufacturer’s proposed labelling. *Id.*

⁵⁹ Nicholas S. Downing et al., *Postmarket Safety Events Among Novel Therapeutics Approved by the US Food and Drug Administration Between 2001 and 2010*, 317 *J. OF THE AM. MED. ASS’N*. 1854, 1855–56 (2017).

⁶⁰ Post-market safety events include market withdrawals, additions of FDA-mandated black box warnings to drug labels and FDA safety communications. *Id.* at 1856.

⁶¹ *Id.* at 1854.

process for generic drugs called the ANDA.⁶² An ANDA requires manufacturers to generate very little new information because generic drugs are copies of NDA-approved new drugs for which extensive safety and effectiveness information was generated and disclosed.⁶³ The only new information required is a small-scale study to prove “bioequivalence,” meaning that the generic drug becomes available at the site of action at the same rate and to the same extent as that of the brand drug.⁶⁴ No new safety information is required.⁶⁵ Again, though, adverse effects arising from generic drug use may only be recognized long after a generic drug’s approval.

Both the NDA and ANDA processes can be seen as mechanisms that force the production and dissemination of a certain quantum of information about drug risk and effectiveness.⁶⁶ This information-forcing serves at least four purposes. First, the information permits the relevant regulator, the staff of the FDA’s Center for Drug Evaluation and Research (CDER), to determine whether the drug meets the substantial evidence standard for approval.⁶⁷ Second, the information allows patients to decide whether to take the prescribed drug in a simplified form.⁶⁸ Third, the information assists payors, such as Medicare and Medicaid, to decide whether to cover the use of

⁶² See generally Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. 98-417, § 101, 98 Stat. 1585 (1984) (codified at 21 U.S.C. § 355 (2018)).

⁶³ See *id.* (stating that applications are based on already approved drugs).

⁶⁴ Jordan Paradise et al., *Evaluating Oversight of Human Drugs and Medical Devices: A Case Study of the FDA and Implications for Nanobiotechnology*, 37 J.L. MED. & ETHICS 598, 601, 622-23 n.28 (2009). The Hatch-Waxman Act imposes on generic drug makers a “duty of sameness.” In addition to bioequivalence, the active ingredient(s) of generic drug must be the same as those in the brand drug that the generic references and the proposed labeling must be identical to the label of the reference drug. 21 U.S.C. § 355 (2008).

⁶⁵ 21 U.S.C. § 355 (2008).

⁶⁶ Other information forcing mechanisms include failure-to-warn claims brought under state tort and products liability law and the FDA’s authority to require post-market reporting and clinical trials. Russell G. Thornton, *Preemption, Tort Reform, and Pharmaceutical Claims, Part Two: Has the Food and Drug Administration Shown It Is Solely Responsible for the Protection of Patients? Can It Do So? Will It Do So?*, 21 BAYLOR UNIV. MED. CTR. 82, 87–89 (2008).

⁶⁷ CONG. RESEARCH SERV., HOW FDA APPROVES DRUGS AND REGULATES THEIR SAFETY AND EFFECTIVENESS 1, 5–6 (Agata Dabrowska & Susan Thaul eds., 2018).

⁶⁸ See *id.* at 20 (outlining that the FDA maintains a “Postmarket Drug Safety Information for Patients and Providers” communications page and that manufacturers are required to develop material for distribution to patients upon drug dispensation (citing 21 U.S.C. § 355-1 (2018)).

drugs for various conditions.⁶⁹ Fourth, and most relevant here, the information assists prescribers as they decide whether to prescribe a drug for a specific patient.⁷⁰ The FDA communicates a distilled version of the information it possesses regarding the effectiveness and risks associated with the use of drugs for approved indications through drug labels.⁷¹

Although it is necessary for the FDA to distill the massive amount of information it possesses about drug safety and effectiveness, the limited amount of information printed on a drug label, even one running to dozens of pages, renders labels' utility quite limited to physicians. Physicians have many other sources of information, including direct access to published studies, expert consensus statements and peer-to-peer communications.⁷² With so much competition, the FDA's drug labels are perceived of by their target audience—physicians—as offering limited value for FDA-approved indications.⁷³

B. Off-Label Uses

A great deal of scholarly attention has been focused on the dangers associated with off-label uses,⁷⁴ but off-label prescribing is an important part of clinical practice. Before engaging with the negative aspects of off-label prescribing, I will first offer two justifications for it.

⁶⁹ *Id.* at 22.

⁷⁰ *Id.* at 19.

⁷¹ *Id.* at 22.

⁷² Healthcare Client Services, *Most Important Sources of Information for Doctors*, KANTAR MEDIA (Mar. 5, 2015), <https://www.kantarmedia.com/us/thinking-and-resources/blog/most-important-sources-of-information-for-doctors>.

⁷³ Jerry Avron & William H. Shrank, *Educating Patients About Their Medications: The Potential and Limitations of Written Drug Information*, 26 HEALTH AFFAIRS 731, 733 (2007); FDA Fiscal Year 2017 Budget Request (C-Span television broadcast Mar. 2, 2016), <https://www.c-span.org/video/?405851-1/hearing-fdas-fiscal-year-2017-budget&start=2575> (comments of then-FDA Commissioner and physician Robert Califf).

⁷⁴ See, e.g., Kesselheim, *supra* note 12, at 226 (providing examples of dangers associated with off-label use of selective serotonin reuptake inhibitor antidepressants and the anti-inflammatory drug Valdecoxib); Joshua M. Sharfstein & Alta Charo, *The Promotion of Medical Products in the 21st Century: Off-label Marketing and First Amendment Concerns*, 314 J. AM. MED. ASS'N. 1795, 1795 (2015); Ryan Abbott & Ian Ayres, *Evidence and Extrapolation: Mechanisms for Regulating Off-Label Use of Drugs and Devices*, 64 DUKE L.J. 377, 377 (2014); Mello et al., *supra* note 17, at 1557.

The first justification is that off-label use is an essential part of medical practice.⁷⁵ Patients present with problems to be addressed. Physicians have certain tools available—therapy, surgery, medications, etc.—that can be used to address those problems. Providers’ conception of the utility of each tool is formed through the synthesis of multiple streams of information, including the results of randomized clinical trials, other published studies and reports, peer-to-peer information exchanges, teachings absorbed during training, longstanding and widely known patterns of use, personal experience treating patients, and information communicated in FDA-approved drug labels.⁷⁶ In the exam room or at the bedside, the key question is whether, based on an evaluation all of the information available at that moment, the balance of the benefits and the risks of using or refraining from using any given tool is sufficient.⁷⁷ This leads providers to discount the importance of seemingly static metrics such as whether the FDA has approved a drug for an indication and to find irrelevant an information source like the FDA-approved drug label when that label does not contain information about many off-label uses.⁷⁸

Off-label prescribing of FDA-approved drugs is one tool available to clinicians.⁷⁹ Data reported in 2003 indicated that, overall, twenty-two percent of all prescriptions were for off-label indications.⁸⁰ In some patient groups, this number may exceed seventy percent.⁸¹ Many of these

⁷⁵ Christopher M. Wittich et al., *Ten Common Questions (And Their Answers) About Off-Label Drug Use*, 87 MAYO CLIN. PROC. 982, 982-83 (2012). This justification is derived largely from my experiences in my former career as a practicing physician.

⁷⁶ See Healthcare Client Services, *supra* note 72 (giving examples of where doctors receive their information).

⁷⁷ Theo Raynor, *The Benefits of Medicines Outweigh the Risks of Treatment – Says Who?*, PHARM. J. (May 22, 2013), <https://www.pharmaceutical-journal.com/news-and-analysis/the-benefits-of-medicines-outweigh-the-risks-of-treatment-says-who/11121573.article?firstPass=false>.

⁷⁸ Wittich et al., *supra* note 75, at 988-89.

⁷⁹ *Id.* at 982.

⁸⁰ Kesselheim, *supra* note 12, at 234.

⁸¹ *Id.* at 236.

uses have become the standard of care.⁸² As medicine is practiced today, off-label use of prescription drugs is both necessary and proper.

The second justification arises from the recognition that off-label prescribing is important to advance medical knowledge. Sometimes drugs have beneficial effects on conditions for which they were not originally approved. Amiodarone, a drug initially approved for the treatment of angina, was found to be far too toxic to be used for that indication.⁸³ However, the drug was found to be remarkably effective at suppressing life-threatening heart rhythm disorders at lower, and thus, safer doses than were required to treat angina.⁸⁴ Faced with patients who were at high risk of sudden cardiac death from heart rhythm disorders, physicians began to prescribe amiodarone for these off-label indications.⁸⁵ Ultimately, this led to amiodarone being studied and approved for the treatment of certain heart rhythm disorders.⁸⁶

These two justifications are sufficient to reject calls for a general ban on off-label prescribing. However, off-label uses undoubtedly pose significant risks. Off-label uses have not been subjected to the information-forcing mechanisms imposed by the new drug application process. This has two major consequences. First, the safety and effectiveness of off-label uses have not been evaluated by the regulator of first resort, the staff of the FDA's CDER. Second, the safety and effectiveness of some off-label uses cannot be evaluated by clinicians. Although some off-label uses are well-supported by clinical trials, many (up to seventy percent by some

⁸² See Tomaszewski, *supra* note 11, at 887-88 (describing the off-label uses of intravenous Mucomyst for acetaminophen overdose, octreotide for sulfonylurea overdose and insulin infusion for verapamil overdose as “doing the right thing”).

⁸³ Yoon-Nyun Kim & Hyoung-Seob Park, *Adverse Effects of Long-Term Amiodarone Therapy*, 29 KOREAN J. INTERNAL MED. 571, 571 (2014); Lylie A. Siddoway, *Amiodarone: Guidelines for Use and Monitoring*, 68 AMER. FAM. PHYSICIAN 2189, 2191-93 (2003).

⁸⁴ Siddoway, *supra* note 83, at 2190.

⁸⁵ See *id.* at 2189 (stating that physicians prescribe amiodarone for heart rhythm disorders).

⁸⁶ *Id.*

estimates) are not.⁸⁷ Quite simply, clinical trial data supporting safety and effectiveness are often lacking.

Anecdotes of the risks associated with off-label drug use are widely discussed⁸⁸ and clinical data demonstrating that off-label use is associated with increased risk are available for certain uses or populations.⁸⁹ However, the association of harm with off-label use has only recently been documented in a broad population sample study published in the *Journal of the American Medical Association*.⁹⁰ Because this study is important to the proposal this paper puts forth, it is worthwhile to set out in some detail.

A group of researchers at McGill University, Harvard Medical School, and the Massachusetts College of Pharmacy and Health Sciences studied over 46,000 adult patients who were seen at clinics in Quebec.⁹¹ The percentage of off-label use in this population varied widely--for example, there was up to 65.6 percent for anticonvulsant drugs.⁹² Adverse events occurred overall at a rate of 13.2 per every 10,000 person-months.⁹³ When stratified for approved and off-label uses, the risks per 10,000 person-months were 12.5 and 19.7, respectively.⁹⁴ This forty-four percent difference was strongly statistically significant, which further provides strong support for the concerns that have been raised about off-label drug use.⁹⁵

⁸⁷ Kesselheim, *supra* note 12, at 234-35.

⁸⁸ *See, e.g., id.* at 226 (providing examples of dangers associated with off-label use of selective serotonin reuptake inhibitor antidepressants and the anti-inflammatory drug valdecoxib).

⁸⁹ *See, e.g.,* Ji-Hyun Lee et al., *Safety and Efficacy of Off-label and Unlicensed Medicines in Children*, 33 J. KOREAN MED. SCI. 1, 1-2 (2018) (presenting evidence that off-label use in children is associated with increased risk).

⁹⁰ Tewodros Eguale et al., *Association of Off-label Drug Use and Adverse Drug Events in an Adult Population*, 176 J. AM. MED. ASS'N INTERNAL MED. 55, 55 (2015).

⁹¹ *Id.*

⁹² *Id.* at 58.

⁹³ *Id.*

⁹⁴ *Id.*

⁹⁵ *Id.* The 95 percent confidence intervals were 1.30-1.60. *Id.*

The researchers further stratified the off-label uses into those that were supported by “strong evidence” and those that were not.⁹⁶ Strong evidence was determined by using a commercially-available algorithm that incorporates the efficacy of the use, the strength of recommendations regarding use, and the strength of evidence (randomized controlled trial [RCT] with consistent results, RCT with inconsistent results, or no RCT).⁹⁷ In their study population, the majority of off-label uses were not supported by strong data: 2.3 percent of all prescriptions were for off-label uses supported by strong data, while 9.5 percent were for off-label uses unsupported by strong data.⁹⁸

The association of a lack of strong evidence with the risk of off-label use is striking. Off-label uses supported by strong evidence were associated with a risk of serious adverse events of 13.2 per 10,000 person-months, which was statistically indistinguishable from the risk of adverse events associated with approved uses.⁹⁹ By contrast, off-label uses unsupported by strong evidence were associated with a risk of serious adverse events of 21.7 per 10,000 person-months.¹⁰⁰ The difference was strongly statistically significant, with off-label uses not supported by strong evidence having a fifty-four percent higher risk of adverse events.¹⁰¹

This study, especially if corroborated by other studies, indicates that not all off-label uses are equivalent. Importantly, a simple metric that assesses the strength of evidence supporting an off-label use stratifies those uses into two categories, one whose risk is indistinguishable from approved uses, and the other with a markedly elevated risk.

C. Off-Label Drug Risk and Effectiveness: FDA Label’s Lack of Information

⁹⁶ Tewodros Eguale et al., *Drug, Patient, and Physician Characteristics Associated with Off-label Prescribing in Primary Care*, 172 ARCHIVES OF INTERNAL MED. 781, 783 (2012).

⁹⁷ *Id.* at 782.

⁹⁸ Eguale et al., *supra* note 90, at 58.

⁹⁹ *Id.* at 58, 59.

¹⁰⁰ *Id.* at 59.

¹⁰¹ *See id.* (reporting multivariate adjusted relative risk).

The FDA last overhauled its regulations governing drug labels in 2006.¹⁰² Despite improvements in the organization, content, and presentation of the information contained in drug labels as a result of the 2006 Final Rule and the guidance statements it spawned, drug labels do not contain any information about off-label uses of approved drugs.¹⁰³ Because many prescriptions are written for off-label indications, for which the FDA does not evaluate effectiveness and safety, the label often fails to provide any useful information at all to many prescribers.

One example of this failure is found in the FDA-approved label for the antiarrhythmic drug Cordarone (generic: amiodarone). The drug was originally approved in 1985 for the prevention of life-threatening heart rhythm disorders involving the ventricles.¹⁰⁴ Individuals who develop a tendency for ventricular tachycardia and ventricular fibrillation can experience palpitations, dizziness, and abrupt loss of consciousness.¹⁰⁵ Most significantly, these arrhythmias can lead to sudden cardiac death.¹⁰⁶ Before implanted defibrillators became feasible for most patients, amiodarone was considered first-line therapy to reduce the risk of ventricular tachycardia and fibrillation.¹⁰⁷ Now that defibrillators are widely available and relatively easy to implant, amiodarone's role in treating ventricular arrhythmias is solely adjunctive.¹⁰⁸

¹⁰² See Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products, 71 Fed. Reg. 3921, 3922 (Jan. 24, 2006) (containing the Final Rule implementing major changes to content and organization of drug labels).

¹⁰³ 21 C.F.R. §201.57 (2015). In rare instances the FDA may require manufacturers to include information about an off-label use in a drug label. However, to do so the Agency must determine that such a use is ineffective under a preponderance of the evidence standard. *Id.*

¹⁰⁴ FDA, Cordarone Highlights of Prescribing Information 1 (FDA eds., 2018), https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/018972s054lbl.pdf [hereinafter FDA Cordarone Highlights].

¹⁰⁵ MAYO CLINIC, *Ventricular Fibrillation*, <https://www.mayoclinic.org/diseases-conditions/ventricular-fibrillation/symptoms-causes/syc-20364523> (last visited Oct. 14, 2019).

¹⁰⁶ Eric Williams & Mohan Viswanathan, *Current and Emerging Antiarrhythmic Drug Therapy for Ventricular Tachycardia*, 2 *CARDIOLOGY THERAPY* 27, 28 (Feb. 20, 2013).

¹⁰⁷ *Id.* at 30.

¹⁰⁸ *Id.* at 29.

Over time, amiodarone has become one of the, if not the, most commonly prescribed drugs used to treat atrial fibrillation, a chaotic disorder of the upper heart chambers.¹⁰⁹ In part, this occurred because evidence emerged showing that other drugs used to treat atrial fibrillation caused an increased risk of sudden cardiac death—they promoted fatal heart rhythm abnormalities, a danger far worse than the abnormality they were prescribed to treat.¹¹⁰ Although amiodarone was known to be toxic to the lungs, liver, thyroid, skin, and other organs, the drug has long been recognized as the most effective drug to suppress atrial fibrillation.¹¹¹ The leading professional societies, the American Heart Association, the American College of Cardiology, and the Heart Rhythm Society, published their most recent joint guidelines for the management of atrial fibrillation in 2014.¹¹² The societies considered amiodarone to be a first line therapy for the prevention of atrial fibrillation.¹¹³

But the drug label for Cordarone, and its generic equivalents, still presents information solely regarding the drug's use for its FDA-approved indications, “[r]ecurrent ventricular fibrillation [and r]ecurrent hemodynamically unstable ventricular tachycardia.”¹¹⁴ Consistent with the prohibition on information about non-approved indications, the label presents no information regarding the use of amiodarone for the condition which the drug has come to be used most frequently, atrial fibrillation.¹¹⁵ The label does not inform prescribers of the effectiveness of amiodarone for atrial fibrillation.¹¹⁶ Nor does the label inform physicians about

¹⁰⁹ Norman Wolkove & Marc Baltzan, *Amiodarone Pulmonary Toxicity*, 16 *CAN. RESPIRATORY J.* 43, 43 (Mar. 2009).

¹¹⁰ Williams, *supra* note 106, at 33.

¹¹¹ Wolkove & Baltzan, *supra* note 109, at 47.

¹¹² CRAIG T. JANUARY ET AL., A REPORT OF THE AMERICAN COLLEGE OF CARDIOLOGY/AMERICAN HEART ASSOCIATION TASK FORCE ON PRACTICE GUIDELINES AND THE HEART RHYTHM SOCIETY 199 (Am. Heart Ass'n et al. eds., 1st ed. 2014).

¹¹³ *Id.* at e233.

¹¹⁴ FDA Cordarone Highlights, *supra* note 104, at 2.

¹¹⁵ *Id.*

¹¹⁶ *Id.*

the risks, which, because the doses are much lower than for ventricular arrhythmias, are lower for the treatment of atrial fibrillation.¹¹⁷ Practicing physicians found it no surprise when then-FDA Commissioner and physician Robert Califf stated in a Senate hearing that, “if you talk to doctors, none of them . . . read drug labels.”¹¹⁸ In an information-rich environment, prescribers find minimal value in FDA drug labels.

II. FDA’s Traditional Approach to Off-Label Drug Activities

The regulation of off-label drug activities might be accomplished by many avenues. State regulatory agencies can, and sometimes do, prohibit physicians from prescribing drugs for certain indications.¹¹⁹ State agencies likely do not have any barriers to promulgating a blanket ban on off-label prescribing.¹²⁰ Congress could prohibit physicians from prescribing and pharmacies from dispensing medications, as is currently done with Schedule I drugs like heroin.¹²¹ Payors, including Medicare and Medicaid, could refuse payment for off-label prescriptions.¹²² In addition, regulation might be accomplished in purely post-hoc fashion through state tort and products liability law actions.

Instead of relying on these mechanisms, the regulation of off-label drug activities has largely fallen to the FDA, but the FDA has had a tortured relationship with off-label drug prescribing and promotion.¹²³ In general, the Agency has eschewed attempts at directly

¹¹⁷ *Id.* at 4, 5.

¹¹⁸ FDA Fiscal Year 2017 Budget Request (C-Span television broadcast Mar. 2, 2016), <https://www.c-span.org/video/?405851-1/hearing-fdas-fiscal-year-2017-budget&start=2575>.

¹¹⁹ *See, e.g.*, *In re Williams*, 573 N.E.2d 638 (Ohio 1991) (noting that state medical board promulgated rule prohibiting prescribing of certain amphetamines for long-term use in weight loss treatment); *see also* Patricia Zettler, *The Indirect Consequences of Expanded Off-Label Promotion*, 78 OHIO ST. L.J. 1053, 1081 (2017) (states have also limited off-label prescribing of certain drugs through legislation and regulation, consistent with states’ long-recognized authority to regulate medical practice pursuant to their police powers).

¹²⁰ *See generally*: *Commonwealth v. Alger*, 61 Mass. 53, 85 (1851) (this would fall under that states’ long-recognized police power to protect the health of its citizens).

¹²¹ *Drug Scheduling*, DEA (last accessed Oct. 9, 2019), www.dea.gov/drug-scheduling.

¹²² *CMA Report: Medicare Coverage For Off-Label Drug Use*, CTR. FOR MEDICARE ADV. (Sept. 2010), www.medicareadvocacy.org/cma-report-medicare-coverage-for-off-label-drug-use/.

¹²³ Wittich et al., *supra* note 75, at 982.

prohibiting physicians from prescribing drugs for off-label indications.¹²⁴ The legislative histories of the Food, Drug, and Cosmetics Act of 1938 (FDCA) and the Drug Amendments of 1962 indicate that Congress did not intend to authorize the FDA to regulate the practice of medicine.¹²⁵ Several later amendments to the FDCA, including the FDA Modernization Act of 1997 and the FDA Amendments Act of 2007 included provisions specifically barring constructions of the FDCA which “limit the practice of medicine.”¹²⁶ In a closely related context, the off-label use of medical devices, the Supreme Court characterized the FDA’s mission as one of regulating “without directly interfering with the practice of medicine.”¹²⁷ Underlying this division of authority over the health care enterprise into state regulation of the practice of medicine and federal regulation of medical products are longstanding notions of federalism.¹²⁸

Rather, the FDA has focused on regulating manufacturers’ off-label promotion.¹²⁹ The FDA’s position has evolved over time, in response to statutory changes enacted by Congress and to court decisions.¹³⁰ The FDCA does not explicitly bar manufacturers from engaging in off-label promotion,¹³¹ but it prohibits the “introduction into interstate commerce any new drug, unless an approval of an NDA or ANDA is effective with respect to such drug.”¹³² Promoting a drug for an unapproved use is considered analogous to introducing the drug into interstate commerce without an NDA or ANDA for that indication, thus violating § 355(a).¹³³ And the FDCA prohibits the

¹²⁴ *Id.*

¹²⁵ Wendy Teo, *FDA and the Practice of Medicine: Looking at Off-Label Drugs*, 41 SETON HALL LEGIS. J. 305, 307-08 (Sept. 5, 2017).

¹²⁶ Food and Drug Administration Modernization Act Of 1997, 21 U.S.C. § 396 (1997); FDA Amendments Act of 2007, 21 U.S.C. §1111 (2007).

¹²⁷ *Buckman Company v. Plaintiffs’ Legal Committee*, 531 U.S. 341, 350 (2001).

¹²⁸ Patricia Zettler, *Toward Coherent Federal Oversight of Medicine*, 52 SAN DIEGO L. REV. 427, 427 (2015).

¹²⁹ Mello et al., *supra* note 17, at 1557.

¹³⁰ *Id.* at 1558.

¹³¹ *Id.*

¹³² 21 U.S.C. § 355 (2008).

¹³³ *Id.* § 352.

introduction into interstate commerce of a drug that is misbranded.¹³⁴ A drug is considered misbranded

[u]nless its labeling bears (1) adequate directions for use; and (2) such adequate warnings against use in those pathological conditions or by children where its use may be dangerous to health, or against unsafe dosage or methods or duration of administration or application, in such manner and form, as are necessary for the protection of users.¹³⁵

The FDA considers all information “distributed by the manufacturer for the purpose of explaining the uses of the drug, even if they are not packaged with the drug.”¹³⁶ Thus, promoting a drug for unapproved uses violates the FDCA’s misbranding provision.

Under these authorities, the FDA has proscribed manufacturers’ off-label promotional activities for decades,¹³⁷ but FDA regulations contain certain safe harbors. For example, manufacturers may distribute peer-reviewed article reprints in response to unsolicited questions from physicians regarding off-label uses and may sponsor unbiased continuing medical education meetings and courses.¹³⁸

The FDA’s attempt to minimize the risks associated with off-label drug prescribing through the policing of off-label promotion is flawed for three reasons. First, banning or severely restricting off-label promotion may deprive physicians of valuable sources of information. Drug manufacturers typically possess the largest amount of information regarding the effectiveness and risks of the drugs they market.¹³⁹ Often the manufacturer has developed the drug, and thus, has a great deal of information from the pre-clinical period. After a drug is marketed, health

¹³⁴ *Id.* § 331.

¹³⁵ Mello et al., *supra* note 17, at 1557.

¹³⁶ *Id.* at 1558.

¹³⁷ Michael Sinha & Aaron S. Kesselheim, *The Next Forum for Unraveling FDA Off-Label Marketing Rules: State and Federal Legislatures*, 15 PLOS MED. 1, 1 (May 8, 2018).

¹³⁸ *Id.*

¹³⁹ Kalyani Sonawane et al., *Serious Adverse Drug Events Reported to the FDA: Analysis of the FDA Adverse Event Reporting System 2006-2014 Database*, 24 J. MANAGED CARE & SPECIALTY PHARMACY 682, 686 (July 2018).

professionals, consumers and drug representatives report adverse effects to the manufacturer, which in turn forwards the reports to the FDA.¹⁴⁰ Physicians also report information to manufacturers about adverse effects informally, through interactions with drug company representatives during “detailing” visits.¹⁴¹ In turn, manufacturers may facilitate the exchange of information among physicians and other health care providers, but these exchanges might be chilled by the threat of prosecution and liability.

Second, the FDA’s approach has had only limited success. Manufacturers continue to promote their drugs for off-label uses. False Claims Act recoveries by the Department of Justice from manufacturers who engaged in off-label promotion give some idea of the scope of the ongoing off-label promotional activities by pharmaceutical companies.¹⁴² Between 2009 and 2016, the Department recovered over \$19 billion related to health fraud.¹⁴³ The bulk of these recoveries came from drug manufacturers who had promoted their drugs for off-label uses to physicians who then prescribed those drugs to Medicare and Medicaid patients.¹⁴⁴ These recoveries involved the off-label promotion of no fewer than twenty-three drugs.¹⁴⁵ As long as the profits that can be anticipated from off-label promotion exceed the anticipated losses from government enforcement actions, companies will be motivated to continue engaging in off-label promotion.

¹⁴⁰ An analysis of reports of serious adverse drug events to the FDA between 2006 and 2014 showed that 72 percent of reports to the FDA were from manufacturers. *See id.*

¹⁴¹ *Id.*

¹⁴² U.S. DEPT. JUSTICE, FACT SHEET: SIGNIFICANT FALSE CLAIMS ACT SETTLEMENTS & JUDGMENTS, FISCAL YEARS 2009-2016, HEALTH CARE FRAUD.

¹⁴³ *Id.*

¹⁴⁴ *See id.* (including but not limited to recoveries from GlaxoSmithKline (\$3 billion), Pfizer (\$2.3 billion), Johnson & Johnson (\$2.2 billion), Abbott Laboratories (\$1.5 billion), Amgen (\$762 million), Allergan (\$600 million), AstraZeneca (\$520 million), and Novartis (\$495 million) arising from off-label promotion).

¹⁴⁵ *See id.* (listing twenty-three drugs as examples).

Further, physicians continue to prescribe drugs for off-label uses that are not supported by strong evidence. As the McGill/Harvard/MCPHS study discussed in Part I.B demonstrates, the great majority of off-label prescriptions written by physicians are for indications that lack strong evidence.¹⁴⁶ To the extent that off-label promotion has driven physicians' off-label prescribing practices, the FDA's strategy has not succeeded.

Third, the FDA's authority to regulate off-label promotion is rapidly being eroded. The trend over the past decade has been for courts to invalidate the FDA's ban on some off-label promotional activities.¹⁴⁷ The FDA and Department of Justice have strategically refrained from challenging these rulings, to avoid establishing a nationwide rule. Some states have enacted laws permitting manufacturers to engage in truthful off-label promotion.¹⁴⁸ Similarly, bills have been introduced in the U.S. Congress that would permit off-label promotion.¹⁴⁹

Thus, the FDA's approach to addressing the risk of off-label drug prescribing by barring off-label promotion may deprive prescribers of valuable information, has failed to prevent off-label promotion, and is in jeopardy of further erosion as courts expand the scope of the commercial speech doctrine.¹⁵⁰

My purpose here is not to argue that the FDA should abandon its attempts to regulate drug manufacturers' off-label promotional activities. Regulating off-label promotion is an important tool the FDA possesses, and should possess, to address the dangers associated with off-label drug use. Rather, my purpose is to argue that a single-minded focus on off-label

¹⁴⁶ Eguale et al., *supra* note 90, at 58.

¹⁴⁷ *See, e.g.*, *United States v. Caronia*, 703 F.3d 149, 180 (2d Cir. 2012) (truthful off-label promotion protected commercial speech under *Central Hudson* test); *Amarin Pharma., Inc. v. U.S. Food & Drug Admin.*, 119 F. Supp. 3d 196, 225–226 (S.D.N.Y. 2015) (same).

¹⁴⁸ *See, e.g.*, H.R. 2382, 2017, 53rd Sess. (Az. 2017) (“Notwithstanding any other law, a pharmaceutical manufacturer or its representative may engage in truthful promotion of an off-label use of a drug.”).

¹⁴⁹ *Sinha & Kesselheim, supra* note 137, at 1.

¹⁵⁰ *Caronia*, 703 F.3d at 180.

promotion is misguided. I propose that the FDA should focus more on providing information to prescribers through a modification of physician-oriented drug labels. Before setting out the details of my proposal in Part IV, Part III examines a few recent proposals that have been made which address the dangers associated with off-label drug use.

III. Existing Proposals to Address Risks Associated with Off-Label Drug Use

Scholars writing in medical and legal literatures have decried the risks associated with off-label drug use.¹⁵¹ Several scholars have formulated proposals directed at mitigating the information deficits associated with off-label drug activities and the risks that off-label drug use entail.¹⁵²

Some scholars have focused on maintaining the FDA's current authority to regulate off-label promotion. Dr. Joshua Sharfstein and Professor R. Alta Charo recently addressed court decisions that have limited the FDA's ability to regulate off-label promotion. Responding to the district court decision in *Amarin Pharmaceuticals, Inc. v. United States Food & Drug Administration*,¹⁵³ which blocked the FDA "from enforcing restrictions on the marketing and promotion of off-label use of the drug icosapentethyl (Vascepa)," Sharfstein and Charo warned that limiting FDA's authority to regulate off-label promotion would bring back "a time of more claims and less evidence."¹⁵⁴ Further, limiting FDA's authority would result in "liberalizing off-label marketing [which] may well lead companies to increasingly forgo key research that truly establishes the safety and efficacy of their products."¹⁵⁵ Sharfstein and Charo focused on courts' role in limiting FDA's regulatory authority, urging that courts not use "the First Amendment to

¹⁵¹ See *id.* at 180; See also Sharfstein & Charo, *supra* note 74, at 1796; See also Abbott & Ayres, *supra* note 74; see also Mello et al., *supra* note 17, at 1557 (all explaining and highlighting both general and specific risks of off-label drug use promotion).

¹⁵² Abbott & Ayres, *supra* note 74, at 378.

¹⁵³ *Amarin Pharma., Inc. v. U.S. Food & Drug Admin.*, 119 F. Supp. 3d 196, 225–26 (S.D.N.Y. 2015).

¹⁵⁴ Sharfstein & Charo, *supra* note 74.

¹⁵⁵ *Id.* at 1796.

undermine core regulatory functions,” which in the prescription drug context involve serious public health risks.¹⁵⁶

Michael Sinha and Aaron Kesselheim highlighted recent state and federal legislative activities which “would give wide latitude to manufacturers engaging in off-label promotion.”¹⁵⁷ They cited Arizona’s Free Speech in Medicine Act, which became law in 2017. This act established that, “a pharmaceutical manufacturer or its representative may engage in truthful promotion of an off-label use of a drug.”¹⁵⁸ If the FDA’s current regulatory bar on off-label promotion remained in effect, the act would almost certainly not survive a preemption analysis.¹⁵⁹ Sinha and Kesselheim postulated that the real purpose of the act was generate just such a challenge, in the hopes of wiping the FDA’s bar off the books.¹⁶⁰

Sinha and Kesselheim also discussed bills that had been introduced into the U.S. Congress, one of which would “create a new safe harbor for ‘scientific exchange’” between manufacturers and prescribers, while another would allow “manufacturers to present information about unapproved uses to formulary or technology review committees that it ‘anticipates could be sufficient’ to support future FDA approval of such unapproved use.”¹⁶¹ The authors strongly urge that legislatures not “unravel current FDA rules relating to off-label promotion.”¹⁶²

Aaron Kesselheim and Michelle Mello provided a roadmap for the FDA to preserve its ability to regulate off-label promotion in a 2014 article¹⁶³ in response to the Second Circuit’s decision in *United States v. Caronia*.¹⁶⁴ In *Caronia*, the Second Circuit held that “the FDA’s

¹⁵⁶ *Id.*

¹⁵⁷ Sinha & Kesselheim, *supra* note 137, at 2.

¹⁵⁸ Arizona H.R. 2382, *supra* note at 148, at 1.

¹⁵⁹ Sinha & Kesselheim, *supra* note 137.

¹⁶⁰ *Id.*

¹⁶¹ *Id.*

¹⁶² *Id.*

¹⁶³ *Id.*

¹⁶⁴ *United States v. Caronia*, 703 F.3d 149, 181 (2d Cir. 2012).

prohibition on promotion of off-label drug uses was inherently suspect under the Constitution's First Amendment protection of commercial speech.”¹⁶⁵ The authors suggest that in the future the FDA should base prosecutions on written (rather than oral) statements, emphasize that the speech was evidence of the manufacturer’s intent to misbrand the drug, and focus on the falsity of the promotional statements.¹⁶⁶ Further, the FDA should “make a stronger case that its regulations meet the criteria of the *Central Hudson* test,”¹⁶⁷ which requires that regulations of commercial speech be narrowly tailored and advance a substantial government interest.¹⁶⁸

Other scholarly works have proposed ways to strengthen the FDA’s ability to regulate off-label promotion. Aaron Kesselheim has proposed a scheme of “scaled regulation” that imposes varying requirements based on how far an off-label use deviates from approved uses.¹⁶⁹ The proposal by Ryan Abbott and Ian Ayres discussed below also employs a scaling mechanism based on how far an off-label use deviates from an approved use, albeit in the service of regulating off-label prescribing.¹⁷⁰ Kesselheim suggested a three-axis measure for the degree of deviation, in which the FDA would consider whether a drug was being used for a different disease, whether it was being used for an indicated disease but in a different manner, and whether it was being used at different doses or dosing intervals.¹⁷¹

Kesselheim’s proposal reaches quite far, requiring that manufacturers obtain FDA approval for off-label uses of their drugs.¹⁷² As off-label uses deviate from approved uses along

¹⁶⁵ 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, 1541 (2014).

¹⁶⁶ *Id.* at 1540.

¹⁶⁷ *Id.* at 1574.

¹⁶⁸ *Id.* at 1555.

¹⁶⁹ Sinha & Kesselheim, *supra* note 12, at 255-56.

¹⁷⁰ Abbott & Ayres, *supra* note 74, at 378

¹⁷¹ Sinha & Kesselheim, *supra* note 12, at 253-54.

¹⁷² *Id.* at 254-55.

more axes, the requirements for FDA approval would be more rigorous.¹⁷³ Off-label uses that deviate only on one axis might be approved through an accelerated pathway. Conversely, more substantial deviations would require more substantial data for approval. In essence, Kesselheim's proposal is to require manufacturers to obtain FDA approval for off-label uses, with the scaled regulation framework serving as way to limit the regulatory burden this requirement places on manufacturers. One important limitation on the implementation of a scaled framework is that the relative importance of Kesselheim's three axes, and possibly other relevant factors, is currently unknown. Thus, a substantial amount of research would need to be completed before such a proposal could be implemented.

In 2014, Professors Ryan Abbott and Ian Ayres put forward an ambitious set of recommendations that focus on off-label prescribing.¹⁷⁴ They divided their recommendations into three general categories, which (1) aimed to correct some of the information deficits that attend off-label drug use, (2) leverage the FDA's recently-enhanced authority to require manufacturers to conduct post-market studies of the risks of off-label uses, and (3) alter prescribing practices by creating three new boxed warnings that the FDA could require on drug labels.¹⁷⁵

As the McGill/Harvard/MCPHS study illustrates, data about the indications for which drugs are prescribed is important, but such data are largely unavailable in the United States. To mitigate this information deficit, Abbott and Ayres proposed that drug manufacturers be required to include in their annual reports to the FDA "a rough breakdown of each approved drug's annual sales by diagnostic code."¹⁷⁶ This, along with a recommendation that the FDA make a de-

¹⁷³ *Id.*

¹⁷⁴ Abbott & Ayres, *supra* note 74, at 378, 409.

¹⁷⁵ *Id.* at 380–81.

¹⁷⁶ *Id.* at 400.

identified version of this information publicly available, could provide the FDA, payors, scholars, and others with a robust set of information regarding patterns of off-label prescribing.

One potential counterargument is that reporting requirements would impose burden in terms of search and reporting costs on manufacturers. Abbott and Ayres suggested that the FDA could allow manufacturers “reporting flexibility” to blunt the potential onerousness of this requirement by imposing a standard that requires manufacturers to report only the information that they know (or should have known after using “reasonable diligence”).¹⁷⁷ Further, they argued that imposing such a requirement would not be unduly burdensome because the manufacturers likely already possessed much of the data that would be required.¹⁷⁸

Abbott and Ayres also proposed that all prescriptions for which reimbursement would be sought from any Medicare and Medicaid program be accompanied by a diagnostic code.¹⁷⁹ Noting that these programs cover one hundred million people in the United States, the authors view this as permitting the assembly of a robust database on prescribing patterns.¹⁸⁰ Indeed, this proposal would complement the reporting obligation on manufacturers that their first recommendation would impose.¹⁸¹

Other scholars have raised concerns that such requirements might lead to fraudulent coding as physicians sought to tailor the diagnostic codes they submit to the currently-approved indications of a drug.¹⁸² This behavior is not uncommon, and is motivated by a desire to ensure that patients can afford to obtain the treatment they need.¹⁸³ Despite a robust array of statutory

¹⁷⁷ *Id.* at 402.

¹⁷⁸ *Id.*

¹⁷⁹ *Id.* at 405-06.

¹⁸⁰ *Id.* at 406.

¹⁸¹ *Id.*

¹⁸² *Id.*

¹⁸³ *Id.*

authorities, including the Anti-Kickback Statute¹⁸⁴ and the False Claims Act,¹⁸⁵ and the possibility of steep and highly public financial penalties for providing false information on a Medicare or Medicaid claim, this type of fraud remains very common.¹⁸⁶ Abbott and Ayres respond “that the professionals in these markets are far more likely to comply with providing diagnostic codes,” placing their faith in “the capacity of the Medicare/Medicaid fraud-prevention apparatus.”¹⁸⁷ However, it is unclear how valuable (or feasible) it is to the government to sanction individual prescribers who provide false diagnostic codes to ensure payment for an indication for which the Centers for Medicare and Medicaid Services (CMS) does not reimburse. Most providers are likely low-value targets in terms of the costs they impose on Medicare and Medicaid. Further, this type of enforcement activity might offend the traditional norms and federalism-based boundaries that afford the states the authority to regulate the practice of medicine.¹⁸⁸

Abbott and Ayres’s second major category of recommendations sought to leverage the enhanced authority over post-market testing that the FDA acquired through the Food and Drug Administration Amendments Act of 2007 (FDAAA).¹⁸⁹ The FDAAA gave the FDA authority to order manufacturers to conduct post-market studies “to assess a known serious risk, to assess

¹⁸⁴ 42 U.S.C. § 1320a-7b(b) (2018).

¹⁸⁵ False Claims Act, 31 U.S.C. §§ 3729-3733 (2009).

¹⁸⁶ Jacqueline LaPointe, *Over 600 Individuals Charged in 2018 Healthcare Fraud Takedown*, REVCYCLE INTELLIGENCE (June 28, 2018), <https://revcycleintelligence.com/news/over-600-individuals-charged-in-2018-healthcare-fraud-takedown>.

¹⁸⁷ Abbott & Ayres, *supra* note 74, at 406-07.

¹⁸⁸ Timothy S. Jost, *Health Care Reform Requires Law Reform*, 28 HEALTH AFF.: WEB EXCLUSIVES (2009), (“[C]onsider[ing] how federal law has limited state health care reforms, how state law impedes federal health reform efforts, and how both constrain innovation in the private sector.”).

¹⁸⁹ Abbott & Ayres, *supra* note 74, at 396, 409.

signals of a serious risk, or to identify an unexpected serious risk.”¹⁹⁰ Abbott and Ayres suggest that the FDA use this authority to force manufacturers to study the risks of off-label uses.¹⁹¹

To decide when to demand post-market studies of an off-label use, Abbott and Ayres suggest that regulators formally apply a multi-factor weighing test similar to Kesselheim’s scaled regulation framework.¹⁹² A non-exclusive list of factors for regulators to consider includes how frequently a drug is used off-label as a percent of all prescriptions, how far the off-label use varies from approved uses, how frequently adverse events occur with off-label use, the risk-benefit trade-offs between non-use and off-label use, and whether a sufficiently large population of candidates for the off-label use exists.¹⁹³

While these proposed factors appear reasonable, they raise a number of problems. First, the frequency threshold that Abbott and Ayres appear to have in mind is large, “perhaps even a majority” of all prescriptions.¹⁹⁴ Even a low-frequency off-label use can result in wide exposure where a drug is very frequently prescribed. Second, understanding how deviations from approved uses relates to the risks off-label use will require a great deal of additional study.¹⁹⁵ Third, the frequency of adverse events and their severity (combining their third and fourth factors)¹⁹⁶ misses one key point: these will only trigger a requirement of post-market study once a risk has been identified. This problem would likely be mitigated by the passive surveillance mechanisms—enhanced reporting, etc.—that constitute the first category of recommendations that Abbott and Ayres put forward.¹⁹⁷ Lastly, the use of risk-benefit trade-offs as an a priori

¹⁹⁰ *Id.* at 396.

¹⁹¹ *Id.* at 409.

¹⁹² *Id.* at 410-11.

¹⁹³ *Id.*

¹⁹⁴ *Id.* at 410.

¹⁹⁵ Sandeep Kumar Gupta & Roopa Prasad Nayak, *Off-Label Use of Medicine: Perspective of Physicians, Patients, Pharmaceutical Companies and Regulatory Authorities*, 5 J. PHARMACOLOGY & PHARMACOTHERAPY 88, 88 (2014).

¹⁹⁶ Abbott & Ayres, *supra* note 74, at 410-11.

¹⁹⁷ *Id.* at 399.

means of determining when to require post-market studies may assume the answer to many of the key questions that those studies could answer.¹⁹⁸

Ultimately, my view of Abbott and Ayres’s recommendations in this category is quite favorable—the FDA should order manufacturers to conduct post-market studies more often than it currently does. My main criticism is that the multifactor analysis they posit is not sufficiently data driven and may lead regulators to require too few post-market studies.

Abbott and Ayres’s final category of recommendations involves the creation of three new boxed warnings that the FDA could require for off-label uses.¹⁹⁹ These warning categories, color-coded red, black, and gray, are portrayed as involving scaled levels of enforcement stringency.²⁰⁰ For all of these categories, off-label promotion would be prohibited.²⁰¹ Further, all prescriptions for a drug falling into any of these categories (including prescriptions for approved indications) would require an accompanying diagnostic code.²⁰²

Gray box warnings are treated as the least stringent.²⁰³ Gray box warnings “should presumptively preclude CMS reimbursement, unless CMS makes a deliberate decision to the contrary.”²⁰⁴ This, as Abbott and Ayres note, would likely affect private insurers’ coverage determinations.²⁰⁵

One problem with the proposed gray box warnings is that the FDA currently lacks the authority to determine coverage decisions, which are made by CMS.²⁰⁶ Other than a small FDA-

¹⁹⁹ *Id.* at 412.

²⁰⁰ *Id.*

²⁰¹ *Id.* at 413.

²⁰² *Id.*

²⁰³ *Id.* at 413-15.

²⁰⁴ *Id.* at 415.

²⁰⁵ *Id.*

²⁰⁶ James D. Chambers et al., *Medicare Covers the Majority of FDA-Approved Devices and Part B Drugs, but Restrictions and Discrepancies Remain*, 32 HEALTH AFF. 1109, 1109 (2013).

CMS pilot program in which the two agencies jointly participated in drug approval and coverage determinations, these decisions are made independently.²⁰⁷ It is likely that one of two changes requiring congressional action would be necessary for this proposal to be effective. Either Congress could empower the FDA to make certain coverage determinations, or Congress could require CMS to abide by the FDA’s gray box determinations.²⁰⁸

Abbott and Ayres’s next level of stringency comes in the form of black box warnings.²⁰⁹ In addition to the ban on off-label promotion, the requirement for diagnostic codes, and the presumptive bar on CMS coverage, off-label prescriptions for drugs in this category could be subjected to various requirements such as a mandate that the prescriber obtain informed consent.²¹⁰

Finally, the most stringent are red box warnings, which would prohibit the “most dangerous and most problematic” off-label uses as well as promotion.²¹¹ To accomplish this, red box warnings would state that “the FDA considers violating a red-box warning conclusive evidence of malpractice and grounds for discipline.”²¹² Abbott and Ayres also suggested the possibility that “a statutory amendment might provide for direct civil liability to the agency.”²¹³

The red box warnings proposal raises concerns that the FDA would be venturing too far into the regulation of the practice of medicine.²¹⁴ Even if one finds this to be normatively

²⁰⁷ *Id.*; *Payor Communication Task Force*, U.S. FOOD & DRUG ADMIN., <https://www.fda.gov/about-fda/cdrh-innovation/payor-communication-task-force> (last updated July 31, 2019).

²⁰⁸ See Chambers et al., *supra* note 206, at 1109 (discussing the different standards the FDA and CMS have regarding decisions to approve and cover new medical technologies and how those differences “have made it difficult to achieve consistency in decision making”).

²⁰⁹ Abbott & Ayres, *supra* note 74, at 414.

²¹⁰ *Id.* at 413, 15.

²¹¹ *Id.*

²¹² *Id.* at 414.

²¹³ *Id.*

²¹⁴ *Id.*; Michael Ollove, *Pressure Mounts to Lift FDA Restrictions On Off-Label Drugs*, WASH. POST: HEALTH SCI. (Oct. 8, 2017), https://www.washingtonpost.com/national/health-science/pressure-mounts-to-lift-fda-restrictions-on-off-label-drugs/2017/10/06/568204a0-a2f6-11e7-8cfe-d5b912fab99_story.html.

desirable, such a statutory change would certainly face fierce resistance from organized medicine and others.²¹⁵ It is likely that even a rulemaking by the FDA to add “malpractice and grounds for discipline” language would be difficult to complete.²¹⁶

Abbott and Ayres provide examples of how their proposed scheme would work.²¹⁷ One concerned the antipsychotic drug Seroquel, which was FDA-approved for schizophrenia and mania-associated bipolar disorder.²¹⁸ Approximately three-quarters of prescriptions for Seroquel are for one of at least eleven off-label indications.²¹⁹ In 2009, the FDA required a black box warning stating that Seroquel was not approved for the treatment of patients with dementia-related psychosis and that use in these patients was associated with an increased risk of death.²²⁰

The Seroquel example highlights some of the advantages of the Abbott and Ayres proposal.²²¹ In spite of FDA advisories and existing black box warnings, physicians continued to prescribe Seroquel and other related antipsychotic drugs in substantial numbers to patients with dementia-related psychosis.²²² Abbott and Ayres’s tiered boxed warning system would impose more stringent controls over the drug’s off-label use.²²³ Under the proposal, Seroquel’s black box warning would have triggered the requirement that all prescriptions be accompanied by a

²¹⁵ Ollove, *supra* note 214; Richard Epstein, *Government Overreach Threatens Lives*, N.Y.U. J.L. & LIBERTY: BLOG (Oct. 2, 2013), <http://lawandlibertyblog.com/nyujll/2013/10/2/government-overreach-threatens-lives>.

²¹⁶ Thomas Sullivan, *FDA: Off Label May Be the Wrong Label*, POL’Y & MED. (May 4, 2018), <https://www.policymed.com/2010/05/fda-off-label-may-be-the-wrong-label.html> (citing Gregory Conko & Henry J. Miller, *Off Target On Off-Label Drugs*, FORBES (May 12, 2010, 4:28 PM), <https://www.forbes.com/2010/05/12/health-care-drugs-medical-opinions-contributors-henry-miller-gregory-conko.html#1a9745f35b0e>).

²¹⁷ Abbott & Ayres, *supra* note 74, at 417-433.

²¹⁸ *Id.* at 419.

²¹⁹ *Id.* at 420. (citing Margaret Maglione et al., *Off-Label Use of Atypical Antipsychotics: An Update*, 43 COMPARATIVE EFFECTIVENESS REVIEWS 20 (2011), <http://www.ncbi.nlm.nih.gov/books/n/cer43/pdf/>. See *id.* at 29–33 (listing treatment for a variety of conditions, some involving off-label uses of antipsychotics)).

²²⁰ *Id.* at 419.

²²¹ *Id.* at 423.

²²² *Id.* at 421 (citing Sudeep S. Gill et al., *Antipsychotic Drug Use and Mortality in Older Adults with Dementia*, 146 ANN. INTERN. MED. 775, 775 (2007)).

²²³ *Id.* at 425

diagnosis code, which would have resulted in a more robust knowledge base about off-label prescribing patterns.²²⁴

This example also highlights some of the limitations of the Abbott and Ayres proposal. One problem is that by the time many of the mechanisms they propose would have been activated, sufficient data would already have existed regarding the risks posed by the use of Seroquel for dementia-associated psychosis.²²⁵ In fact, in 2010 a metaanalysis showed no effectiveness and an increased risk of death in this population.²²⁶ At this point the relevance of a clinical trial, which the authors recognize would likely be unethical, would have been minimal.²²⁷

A final problem is the volume of work the proposal could add to an already overtaxed administration. Abbott and Ayres's proposal calls for the FDA to conduct an individualized assessment of each off-label use in order to determine whether to require post-market studies.²²⁸ Abbott and Ayres listed at least eleven off-label uses for Seroquel.²²⁹ Considering the historical staffing and funding deficits under which the Agency has labored, adding multiple in-depth data analyses and potentially many post-market studies to follow up seems unlikely to be workable.²³⁰

IV. A Proposal for Reducing the Risks of Off-Label Drug Use

Based on foregoing discussion, I can now begin to lay out the features of a proposal for addressing the risks of off-label drug use. I consider the following features necessary:

- A shift of focus away from off-label promotion toward off-label prescribing;

²²⁴ *Id.* at 413

²²⁵ *Id.* at 414.

²²⁶ *Id.* at 425.

²²⁷ *Id.*

²²⁸ *Id.* at 424.

²²⁹ *Id.* at 420.

²³⁰ Judith Alphonse et al., *The FDA Funding Crisis*, 30 J. PHARM. TECHNOL. 57, 59 (2014) (discussing the dire need of the FDA for increased funding); *FDA Lacks Funding, Staffing to Properly Regulate Pharmaceutical Compounds, Top Agency Official Claims*, KHN MORNING BRIEFING (Sept. 24, 2018), <https://khn.org/morning-breakout/fda-lacks-funding-staffing-to-properly-regulate-pharmaceutical-compounds-top-agency-official-claims/>.

- Use of a mechanism to distinguish between relatively safe and unsafe off-label drug uses;
- Sensitivity to the burdens that would be imposed on the FDA and drug manufacturers;
- Feasibility of implementation without extensive additional research; and
- Simplicity.

There are also several desirable factors. These include:

- The involvement of parties with superior access to information about the frequency of off-label prescribing, notably drug manufacturers;
- The involvement of parties who control off-label prescribing, notably physicians; and
- Providing greater access to the extensive data and expertise possessed by the FDA.

A. Proposal

This Article proposes a “soft power” approach that the FDA might take to address the dangers created by off-label drug activities. Rather than attempting to ban manufacturers’ off-label promotion and providers’ off-label prescribing, the FDA should focus on providing information about the available clinical data concerning the risks and benefits of qualifying off-label uses. Specifically, this Article proposes that once off-label prescriptions account for a certain volume or percentage of a drug’s total prescriptions, a duty to disclose should be imposed on the drug’s manufacturer.²³¹

The manufacturer has the duty to disclose to the FDA all clinical trials, experiences, expert consensus statements, and other information that bears on the risks and benefits of the drug’s off-label use. The manufacturer would have to disclose all information which the manufacturer knows or should know based on reasonable diligence. This disclosure obligation

²³¹ One potentially difficult situation might arise where more than one version of the same drug, such as a brand and at least one generic, is on the U.S. market. It is possible that only one form might exceed the thresholds which would trigger the duty to disclose. Alternatively, the thresholds might be reached only by the combined off-label prescriptions written for some or all versions of the drug. In the former situation the reporting obligations and the inclusion of the level-of-evidence rating would likely need to apply to all manufacturers of that drug. This would avoid running afoul of the requirement that generic drug labels be identical to the label of the reference brand drug. The latter possible situation suggests that the FDA should consider both aggregated and disaggregated prescription totals.

might be implemented in a manner analogous to that suggested by Abbott and Ayres's first set of recommendations.²³² The additional burden imposed by the reporting and disclosure requirements should not be excessive because manufacturers already possess much of this information.²³³

The FDA would not make a risk-benefit determination as it does for NDA applicants. Rather, the Agency would evaluate the strength of the evidence that supports the off-label use. Such an evaluation might be performed by the use of an existing algorithm, such as the program used by the McGill/Harvard/MCPHS researchers.²³⁴ This algorithm has been shown to stratify off-label uses into those with strong support and those without strong support;²³⁵ importantly, this stratification separates off-label uses into high-risk uses and those the risks of that are approximately the same as the risks of FDA-approved indications.²³⁶ In further developing this proposal, a closer examination of the algorithms that the McGill/Harvard/MCPHS researchers used will be necessary.

The advantage of using such "off-the-shelf" programs is that this proposal would be relatively simple to implement. Based on the FDA's evaluation, the Agency would assign a "level of evidence" rating. Medical professional societies routinely use such ratings to communicate to providers the strength of evidence supporting a given use of a drug or procedure.²³⁷ One possible implementation would be a simple "Supported by Strong Evidence" or "Not Supported by Strong Evidence" binary, analogous to the division used in the

²³² See Abbott & Ayres, *supra* note 74, *supra*, notes 174, 176 & 181 and accompanying text.

²³³ *Id.* at 408.

²³⁴ Eguale et al., *supra* note 90, at 55, 63 (study evaluating and monitoring off-label use of prescription drugs and its effect on [adverse drug events] in an adult population).

²³⁵ *Id.* at 56-57.

²³⁶ *Id.* at 59.

²³⁷ Opeyemi O. Daramola, *Rating Evidence in Medical Literature*, 13 *AMA J. ETHICS* 46, 46 (2011).

McGill/Harvard/MCPHS study.²³⁸ This would include an assessment of clinical trial data, real-world experience, and official professional society recommendations. Another possible implementation would contain finer-grained distinctions, more like the rating systems used by medical professional societies,²³⁹ based solely on clinical data.

It is important to distinguish level-of-evidence ratings from “clinical indication” ratings. The latter inform physicians of an expert panel’s consensus recommendation as to whether a particular treatment is indicated for a specific indication.²⁴⁰ The former informs physicians of the strength of the evidence that supports the clinical recommendation.²⁴¹ One danger of the proposal is that physicians and others might interpret a Supported by Strong Evidence rating to mean that the evidence supports the off-label use. Thus, adoption of this proposal would make it necessary to educate physicians and others as to exactly what the FDA-assigned level of evidence was attempting to communicate.

The key educational component would be to distinguish between FDA approval of a drug for a given on-label indication and an FDA rating of Supported by Strong Evidence. FDA approval indicates that the Agency has found the manufacturer had conducted “adequate tests by all methods reasonably applicable to show whether or not such drug is safe for use under the conditions prescribed,” and had presented “substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed.”²⁴² In essence, FDA approval means the Agency has conducted a thorough risk-benefit assessment based on the basic

²³⁸ Egualé et al., *supra* note 90 and accompanying text.

²³⁹ Opeyemi, *supra* note 237, at 59.

²⁴⁰ See Rolla Edward Park et al., *Physician Ratings of Appropriate Indications for Six Medical and Surgical Procedures*, 76 AM. PUB. HEALTH ASS’N 766, 766 (1986) (demonstrating the method of several panels of physicians rating the appropriateness of a large number of indications for performing medical and surgical procedures).

²⁴¹ Opeyemi, *supra* note 237, at 59.

²⁴² 21 U.S.C. § 355(b) (2018).

science, preclinical, and clinical trial data.²⁴³ By contrast, a rating of Supported by Strong Evidence would indicate that based on a holistic review that was simultaneously more inclusive and less stringent than the FDA’s formal approval. Such a rating would not indicate that the FDA had completed a thorough risk-benefit assessment.

One final aspect that this proposal addresses is where the level of evidence rating should be displayed on the drug label. As of the 2006 revisions, FDA drug labels begin with a one-page “Highlights of Prescribing Information.”²⁴⁴ This page displays the drug’s names, approval date, black box warnings, and sections containing notifications of recent changes, approved indications and usage, dosage and administration, dosage forms and strengths, contraindications, warnings and precautions, adverse reactions, drug interactions, and in specific populations.²⁴⁵ This is followed by the “Full Prescribing Information,” divided into as many as seventeen sections.²⁴⁶ Relevant here are the sections containing full information about indications and usage, contraindications, and warnings and precautions.²⁴⁷

The FDA displays information about off-label drug uses in the “Warnings and Precautions” section only in the rare instances in which the preponderance of evidence demonstrates a lack of effectiveness.²⁴⁸ However, the purpose of the proposal put forth here is to inform physicians’ prescribing practices more broadly. As studies have consistently shown,

²⁴³ *Id.*

²⁴⁴ See 21 C.F.R. § 201.56 (2015) (requiring manufacturers to label prescription drugs with specific section headings and content).

²⁴⁵ *Id.*

²⁴⁶ *Id.*

²⁴⁷ Other sections of the Full Prescribing Information are dosage and administration, dosage forms and strengths, adverse reactions, drug reactions, use in specific populations, overdose, description, clinical pharmacology, nonclinical toxicology, clinical studies, how supplied, and patient counseling information.

²⁴⁸ Abbott & Ayres, *supra* note 74, at 385.

physicians are often unaware that they are prescribing in an off-label fashion.²⁴⁹ They likely believe they are prescribing in a safe and effective manner.²⁵⁰ Therefore, the “Warnings and Precautions” section is not a useful place for the level-of-evidence rating. Rather, I propose that the level of evidence rating should either be included in a new, separate section (“Information of Common, Unapproved Uses”), or in a new subsection of the “Indications and Usage” section. The rating should also be included on the “Highlights” page for maximum visibility. This would require a rulemaking by the FDA to accomplish.

This proposal harnesses physicians’ capacities as learned intermediaries and their awareness of the threat of liability for negligence or malpractice. The maxim “first, do no harm” encapsulates many facets of physicians’ inclinations, training, socialization, and practice. Providing physicians with information, especially information that an off-label use, no matter how widely accepted, is not supported by strong evidence should serve at a minimum as a stimulus to look at the clinical data. In fact, the effectiveness of the proposal might be strengthened by including access to the clinical information submitted to the FDA, as through a hyperlink on an electronic version of the drug label.

B. Potential Issues Raised by the Proposal

This proposal raises a number of questions, including (1) whether the FDA could implement it without a statutory amendment to the FDCA, (2) whether including information on the drug label about off-label uses would be equivalent to allowing manufacturers to promote those uses, and (3) how the level-of-evidence assignment would interact with state malpractice, tort, and products liability law? For the moment I assume that the answers to the first two

²⁴⁹ Patti Neighmond, *That Prescription Might Not Have Been Tested for Your Ailment*, NPR: SHOTS – MORNING EDITION (May 12, 2014, 3:24 AM), <https://www.npr.org/sections/health-shots/2014/05/12/307747891/that-prescription-might-not-have-been-tested-for-your-ailment>.

²⁵⁰ *Id.*

questions are favorable to the implementation of the proposal. As to the FDA’s statutory authority, the FDCA gives the Agency the power to require manufacturers to include sufficient information to ensure that a drug may safely be used.²⁵¹ The FDA already mandates the inclusion of information adverse to the commercial interests of manufacturers (through the existing black-box warning requirements and, more recently, warnings about certain off-label uses); requiring a level of evidence rating does not seem to be substantially different.²⁵² As to the possibility of manufacturers using the proposed system to engage in off-label promotion, presenting evidence that an off-label use is not supported by evidence is counter to the manufacturer’s interest in increasing sales. Where a drug has strong evidence to support an off-label use, channeling at least some off-label promotion into a format that is strictly controlled by the FDA (the drug label) may be more desirable than the impossible to control promotion that takes place at medical conferences sponsored by the manufacturer.²⁵³ However, both of these questions need further consideration.

The question of how the level of evidence rating would interact with state malpractice law is important because of the risk of malpractice liability that would arise from an official statement about the quality of the clinical data underlying off-label drug uses might be a powerful motivator of physician prescribing behavior.²⁵⁴ At present, FDA-approved labels do not

²⁵¹ Abbott & Ayres, *supra* note 74, at 382 (citing *Whitney v. California*, 274 U.S. 357, 377 (1927)) (“If there be time to expose through discussion the falsehood and fallacies, to avert the evil by the processes of education, the remedy to be applied is more speech, not enforced silence.”).

²⁵² *Prescription Drug Labeling Resources*, U.S. FOOD & DRUG ADMIN. (last updated Oct. 23, 2014), <https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information> (outlining the labeling resources for the Prescribing Information, FDA-approved patient labeling, and carton and container labeling for human prescription drugs).

²⁵³ Michelle Mello, David Studdert, and Troyan Brennan have described how some communications about off-label drug use are highly visible to the FDA while other communications are virtually invisible. Presentations at conferences fell into an intermediate level of visibility, while presentations and oral statements were at the lowest level of visibility. An FDA-approved label would obviously be highly visible to the Agency. Mello et al., *supra* note 17, at 1557

²⁵⁴ See Kesselheim & Mello, *supra* note 164, at 1596 (describing physician awareness of malpractice liability risks).

include information about off-label uses.²⁵⁵ This absence of information, however, is neither dispositive nor even usually important in establishing whether an off-label use violated the standard of care.²⁵⁶ Rather, off-label uses that are accepted by the relevant medical community are considered consistent with the standard of care.²⁵⁷ This is established by expert testimony. An FDA-approved label that provides a statement that the quality of data underlying an off-label use was poor could serve as one piece of evidence in support of a plaintiff's expert's opinion that the off-label use violated the standard of care, and might provide the means of impeaching a defense expert's testimony.²⁵⁸ Unlike proposals for the FDA to ban certain off-label uses, these applications of the level of evidence rating seem far removed from the regulation of medicine by the FDA that would result from a red box warning.²⁵⁹

The level-of-evidence rating also raises potential issues regarding the liability of manufacturers under state tort and products liability failure to warn claims. Although the proposed level of evidence rating raises interesting preemption questions, in states that have adopted the learned intermediary doctrine this question may be moot.²⁶⁰ Under the learned intermediary doctrine, a drug manufacturer's duty to warn extends only to the prescribing physician.²⁶¹ A "Not Supported by Strong Evidence" level-of-evidence rating on a drug label directed toward physicians might be construed as an adequate warning against the off-label use. If this is so, physicians, not drug manufacturers, would face liability for certain off-label uses of

²⁵⁵ Prescription Drug Labeling Resources, *supra* note 252.

²⁵⁶ Wittich et al., *supra* note 75, at 987.

²⁵⁷ *Id.*

²⁵⁸ *Id.*

²⁵⁹ See Abbott & Ayres, *supra* note 74 and accompanying text.

²⁶⁰ Bexis, *The Learned Intermediary Rule in Consumer Protection Claims*, DRUG & DEVICE L. (Oct. 10, 2016), <https://www.druganddevicelawblog.com/2016/10/the-learned-intermediary-rule-in-consumer-protection-claims.html>.

²⁶¹ *McLeod v. Sandoz, Inc.*, No. 4:16-CV-01640-RBH, 2017 WL 1196801, at *9 (D.S.C. Mar. 31, 2017).

drugs.²⁶² This outcome is consistent with the overall goals of my proposal. The FDA can still attempt to regulate manufacturers' off-label promotion. By incorporating a level-of-evidence rating, the FDA could also create incentives (short of directly attempting to regulate the practice of medicine) for physicians to eschew unsupported off-label prescribing.

One final objection, which goes to the core of my proposal, is that adding a level-of-evidence indication on FDA labels, to which prescribers currently ascribe only limited value, would provide no real incentive to alter prescribing practices. In short, if prescribers do not read drug labels, why would an additional warning make a difference? I offer two responses. The first is that if, as I expect, label statements that a warning is not supported by strong evidence become useful in negligence and malpractice actions, prescribers would be motivated to check this part of a drug label. Being a succinct binary or level, this would involve minimal time and effort. And once a liability-averse prescriber becomes aware of a not-supported statement, the next step would be to investigate the quality of the underlying data on which the statement was based. By simply providing information, this proposal seeks to avoid even the appearance of directly forbidding a practice.

The second response recognizes that providers currently do not read labels. This is exactly why I am proposing that drug labels include information about off-label uses: there is a profound irony that a document structured by the entity (the FDA) with the most information about and expertise in evaluation drug risks is devalued by prescribers. By providing more information, my hope is that drug labels may be seen as a valuable resource.

Conclusion

²⁶² *Id.*

Physicians commonly prescribe drugs for indications that have not been approved by the FDA. Although this practice is necessary and appropriate, many off-label prescriptions are for indications for which there is no strong supporting data. Data from a large recent study indicates that the risk of serious adverse events associated with these prescriptions is much higher than with prescriptions written for approved indications and for prescriptions written for off-label indications with strong supporting data.²⁶³ Off-label prescribing thus constitutes a significant public health risk.

The FDA's traditional approach to minimizing this risk has been to restrict drug manufacturers' off-label promotional activities. But this approach has achieved only limited success and is facing increasing judicial resistance as courts expand the commercial speech doctrine. This Article begins the formulation of an alternative approach, one which focuses more on altering physicians' off-label prescribing practices.

The approach outlined here is one in which the FDA would inform physicians of the strength of evidence that supports common off-label drug uses. When an off-label use exceeds a certain threshold, either in the number or percent of prescriptions written for that drug, the manufacturer would be obligated to provide the FDA all available information about the use. The FDA would then determine the strength of the supporting evidence for that use, and would display that determination prominently on the drug label. This would provide prescribers with a concise statement of the Agency's expert analysis of whether common off-label uses are supported by strong evidence. The goal is that by improving communication between the FDA and prescribers, the risks associated with off-label drug use may be reduced while avoiding direct federal regulation of medical practice.

²⁶³ Eguale et al., *supra* note 90.