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## A Dangerous Concoction: Pharmaceutical Marketing, Cognitive Biases, and First Amendment Overprotection

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# A DANGEROUS CONCOCTION: PHARMACEUTICAL MARKETING, COGNITIVE BIASES, AND FIRST AMENDMENT OVERPROTECTION

CYNTHIA M. HO\*

*This Article argues that pharmaceutical marketing to doctors should be more critically evaluated and entitled to less First Amendment protection, contrary to a trend dating back to the Supreme Court's 2011 decision in Sorrell. In particular, the Article argues that more information to doctors in the form of pharmaceutical marketing does not necessarily result in better patient outcomes. The Article adds a significant critique based on the existence and impact of cognitive bias literature that has thus far not been recognized in this area. If courts fully embrace this understanding, they should recognize that the government, through the Food and Drug Administration, has a right to limit statements that may encourage doctors to prescribe unapproved uses of drugs with potentially fatal consequences.*

*This Article reveals that recent expansion of First Amendment jurisprudence is based on key cognitive biases and assumptions. First, courts, and even some doctors themselves, improperly assume that doctors are adequately sophisticated, such that doctors are protected from self-interested marketing, which this Article demonstrates as inconsistent with reality. Second, current case law assumes that the availability of more information necessarily promotes better decisions so long as it is not patently false, a proposition that this Article shows is especially unfounded in the unique market of prescription drugs. Importantly, such assumptions can have critical health consequences since they promote uses of drugs for which there is often inadequate scientific basis and serious health consequences.*

*Finally, this Article builds upon the revealed cognitive biases to suggest empirically-informed changes to cabin the expansion of First Amendment protection of pharmaceutical marketing as well as broader structural reform. This Article proposes to treat potentially misleading information differently than entirely truthful speech, thus giving states greater discretion to regulate potentially misleading information. In addition, this Article proposes that the burden of proof in such cases should be reversed, so that courts will no longer consider disclaimers as a true alternative to speech restriction without proof that companies will actually promote more informed decisions. The Article also suggests structural changes to medical education, drug development, and marketing informed by the cognitive biases revealed here.*

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\* Clifford E. Vickrey Research Professor, Loyola University Chicago School of Law. This Article benefitted from comments by participants at ASMLE 2017, the Wiet 2017 Life Sciences Conference, and a 2018 Loyola faculty workshop. Thanks to Leah Chan Grinvald, Dmitry Karshtedt, Joan Krause, Christopher Robertson, and Sarah Waldeck for comments on earlier drafts. Extra special thanks go to Jordan Paradise and Nadia Sawiki for providing incredibly helpful feedback and support on multiple drafts. This Article also benefited from the research and editorial assistance of Teresa Gaglione, Austin Holler, Sarah Johnson, Ted Mahan, Monika Malek, Catie Eubanks, Kate Finch, and Cameron Wooley.

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## INTRODUCTION

Is more information always better? First Amendment commercial speech jurisprudence takes this as a given.<sup>1</sup> However, when information is only available from a self-interested and marketing-savvy pharmaceutical company, more information may simply lead to more *misinformation*. Notably, doctors are also misled. This can result in public health harms when companies are promoting unapproved uses of prescription drugs that the Food and Drug Administration (FDA) has approved for other purposes—commonly referred to as “off-label” uses. Contrary to judicial presumptions, as well as the presumptions of some doctors and scholars, doctors are *not* sophisticated enough to always discern what is true versus misleading information. Doctors are susceptible to the same largely unconscious cognitive biases as all individuals;<sup>2</sup> this means that they operate on “schemas” (mental presumptions) that impact how they interpret marketing information.<sup>3</sup> Courts also rely on schemas about how doctors interact with marketing. These schemas have contributed to a First Amendment jurisprudence that has serious consequences for public health because it fails to account for how doctors actually interact with marketing of off-label uses, and such uses are associated with adverse health consequences.

This Article argues that pharmaceutical marketing, especially regarding “off-label” uses, should be more critically evaluated and entitled to less First Amendment protection—contrary to recent court trends, beginning with the 2011 Supreme Court case *Sorrell v. IMS Health Inc.*<sup>4</sup> In other words, this Article is taking a new approach to address court cases that a number of scholars have criticized as unduly expanding the scope of First Amendment protection for pharmaceutical marketing with negative

1. *E.g.*, *Peel v. Attorney Registration & Disciplinary Comm’n of Ill.*, 496 U.S. 91, 110 (1990); *In re R.M.J.*, 455 U.S. 191, 206 n.20 (1982); *Bates v. Arizona*, 433 U.S. 350, 374–75 (1977) (rejecting suggestion that public is better off with incomplete, but correct, information versus potentially misleading information in the context of attorney advertising).

2. *See infra* Section II.A.

3. The term “schema” is used here to refer to an organizing mental framework for processing information. *See* MARTHA AUGOSTINOS, IAIN WALKER & NGAIRE DONAGHUE, *SOCIAL COGNITION: AN INTEGRATED INTRODUCTION* 68–69 (3d ed. 2014).

4. 564 U.S. 552 (2011); *see* *United States v. Caronia*, 703 F.3d 149 (2d Cir. 2012); *Amarin Pharma, Inc. v. FDA*, 119 F. Supp. 3d 196 (S.D.N.Y. 2015); *see also infra* Section III.A.1 (explaining expansion of commercial free speech through these cases).

policy repercussions for public health.<sup>5</sup> Not only are many off-label uses medically unsupported, but permitting broader promotion of such uses undermines incentives for companies to scientifically study those uses.<sup>6</sup> Whereas prior articles have tended to focus on how to adapt to the new law<sup>7</sup> or advocate rejecting the existing law based primarily on policy grounds,<sup>8</sup> this Article uses cognitive bias literature to explain

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5. E.g., Stephanie M. Greene, *After Caronia: First Amendment Concerns in Off-Label Protection*, 51 SAN DIEGO L. REV. 645 (2014); Loren Jacobson, *Don't Fix What Ain't Broken – Off-Label Marketing, the FDA's Regulatory Regime, and the First Amendment*, 5 EMORY CORP. GOV & ACCOUNTABILITY REV. 19 (2018); Aaron S. Kesselheim, Michelle M. Mello & Jerry Avorn, *FDA Regulation of Off-Label Drug Promotion Under Attack*, 309 J. AM. MED. ASS'N 445 (2013); David Orentlicher, *Off-Label Drug Marketing, the First Amendment, and Federalism*, 50 WASH. U. J.L. & POL'Y 89 (2016); Joshua M. Sharfstein, *Public Health and the First Amendment*, 93 MILBANK Q. 459 (2015); Patricia J. Zettler, *The Indirect Consequences of Expanded Off-Label Promotion*, 78 OH. ST. L.J. 1053 (2017). Of course, there are also some scholars that embrace the judicial expansion of First Amendment rights. E.g., Coleen Klasmeier & Martin H. Redish, *Off-Label Prescription Advertising, the FDA and the First Amendment: A Study in the Values of Commercial Speech Protection*, 37 AM. J.L. & MED. 315 (2011); Lars Noah, *The Little Agency That Could (Act with Indifference to Constitutional and Statutory Strictures)*, 93 CORNELL L. REV. 901 (2008); Rodney A. Smolla, *Off-Label Drug Advertising and the First Amendment*, 50 WAKE FOREST L. REV. 81 (2015). In addition, others argue for further expansion. E.g., Jeffrey Chasnow & Geoffrey Levitt, *Off-Label Communications: The Prodigal Returns*, 73 FOOD & DRUG L.J. 257 (2018); Christina Sandefur, *The FDA's Approach to Off-Label Communications: Restricting Free Speech in Medicine?*, REG. TRANSPARENCY PROJECT (May 10, 2018), <https://regproject.org/paper/fdas-approach-off-label-communications-restricting-free-speech-medicine> [<https://perma.cc/FR5B-29CQ>]; see also Carl Wiersum, *No Longer Business as Usual: FDA Exceptionalism, Commercial Speech, and the First Amendment*, 73 FOOD & DRUG L.J. 486 (2018) (arguing FDA rules regarding off-label promotion as well as claims for dietary supplements and graphic cigarette warnings are inconsistent with First Amendment).

6. E.g., Zettler, *supra* note 5; Memorandum from the Food & Drug Admin. on Pub. Health Interests and First Amendment Considerations Related to MFR. Comm'ns Regarding Unapproved Uses of Approved or Cleared Med. Prods. 4–5 (Jan. 2017) [hereinafter FDA Memorandum].

7. E.g., Constance E. Bagley, Joshua Mitts & Richard J. Tinsley, *Snake Oil Salesmen or Purveyors of Knowledge: Off-Label Promotions and the Commercial Speech Doctrine*, 23 CORNELL J.L. & PUB. POL'Y 337 (2013) (providing suggestions for FDA regulation after *Caronia* that arguably meet the stricter heightened scrutiny announced in *Sorrell*); Aaron S. Kesselheim & Michelle M. Mello, *Prospects for Regulation of Off-Label Drug Promotion in an Era of Expanding Commercial Speech Protection*, 92 N.C. L. REV. 1539 (2014) (providing suggestions for future FDA action since *Caronia*).

8. E.g., Orentlicher, *supra* note 5, *passim* (arguing that courts should reject the reasoning of *Caronia*); Christopher Robertson, *The Tip of the Iceberg: A First Amendment Right to Promote Drugs Off-Label*, 78 OH. ST. L.J. 1019 (2017) (challenging arguments in favor of off-label marketing and noting that if these are adopted, all premarket approval of drugs are at risk and also undermine other statutory regimes beyond the FDA); Christopher Robertson & Aaron S. Kesselheim, *Regulating Off-Label Promotion – A Critical Test*, 375 NEW ENG. J. MED. 2313, 2314 (2016) (arguing that courts should reject *Caronia* on its merits and that the FDA, not courts, should be evaluating whether corporate claims are valid); Christopher Robertson & Victor Laurion, *Tip of the Iceberg II: How the Intended-Uses Principle Procedure Medical Knowledge and Protects Liberty*, 11 N.Y.U. J.L. & LIBERTY 770 (2017) (explaining why

why recent cases actually fail to achieve key First Amendment goals. This Article further provides an empirically supported argument against expansion of First Amendment law for off-label promotion.

Marketing of off-label uses is a unique area where First Amendment commercial law concepts may not work well because of an essentially imperfect market. As will be explained, commercial law jurisprudence recognizes commercial speech as valuable to listeners to the extent it provides information. Even though the law realizes some information is potentially misleading, it errs on the side of permitting such information on the assumption that the marketplace of ideas can provide competing information.<sup>9</sup> However, there is no functioning marketplace of ideas with new drugs. Drugs are developed and sold initially only by self-interested companies who must provide clinical data to the FDA, but not to the public.<sup>10</sup> Manufacturers of competing drugs for the same condition do not contribute to a functioning marketplace of ideas because companies tend to only promote attributes of their own drug, but not in comparison to others; this is likely because regulations do not require a drug be superior to existing treatments.<sup>11</sup> Accordingly, the only objective source of information would be from independent scientists unassociated with self-interested companies seeking approval. However, it takes years before independent scientists can evaluate already approved drugs. Sometimes independent scientists will find important caveats to the initial assertions.<sup>12</sup> This is not entirely surprising since the data submitted to the FDA is developed by the self-interested company.<sup>13</sup> However,

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existing FDA regulation are important to produce information and that it functions similar to other regulations). There is also substantial scholarship questioning expansion of First Amendment commercial speech, including *Sorrell*. *E.g.*, Julie E. Cohen, *The Zombie First Amendment*, 56 WM. & MARY L. REV. 1119 (2015); Amanda Shanor, *The New Lochner*, 133 WIS. L. REV. 133 (2016).

9. *See, e.g., supra* note 1.

10. *See infra* Section I.A.

11. *E.g., infra* note 33; *see also* Richard A. Friedman, *What Drug Ads Don't Say*, N.Y. TIMES (April 23, 2016), <https://www.nytimes.com/2016/04/24/opinion/sunday/what-drug-ads-dont-say.html> [<https://perma.cc/5MZP-UVEZ>] (noting that most “new” drugs are unlikely to “substantially outperform” existing drugs). Even when companies tout a feature of their drug, it may misleadingly suggest that this is an improvement when in fact other companies simply did not seek similar approval. *E.g.*, CYNTHIA M. HO, ACCESS TO MEDICINE IN THE GLOBAL ECONOMY: INTERNATIONAL AGREEMENTS ON PATENTS AND RELATED RIGHTS 31 (2011) (explaining that Zyrtec was marketed as the first approved allergy drug for indoor and outdoor allergies even though other allergy drugs are effective for this purpose as well). In addition, companies may intentionally not conduct studies in comparison to other drugs for fear that their drug may perform suboptimally. *See, e.g.*, Ron Winslow, *For Bristol-Myers, Challenging Pfizer Was a Big Mistake*, WALL ST. J. (Mar. 9, 2004, 12:01 AM), <https://www.wsj.com/articles/SB107876021684949151> [<https://perma.cc/X76M-V2HH>] (noting that companies rarely do such studies in the context of discussing Bristol Myers Squibb's failed attempt to establish that its cholesterol-lowering drug compared well to Pfizer's Lipitor).

12. *See infra* Section I.A.

13. Some have suggested that given public interests, it would be better for the government to pay for clinical trials and create independence. *E.g.*, STAN FINKELSTEIN & PETER TEMIN, REASONABLE RX: SOLVING THE DRUG PRICE CRISIS (2008); Tracy R. Lewis, Jerome H.

before independent scientists can do their own studies, corporate marketing lacks any counterbalance. Moreover, although the claims are allegedly based on scientific facts, it is nonetheless possible to selectively present facts. Even if doctors are aware of the financial incentives to misrepresent, given the lack of competing information, they may nonetheless be influenced by these “facts.” This is especially true since cognitive bias literature shows that repeated facts are often presumed true.<sup>14</sup>

The time is ripe to address the existence and impact of largely subconscious cognitive biases to First Amendment case law. Other areas of the law and regulation are increasingly recognizing that subconscious cognitive biases should be given more credence;<sup>15</sup> for example, the Obama Administration issued an Executive Order to use insights from behavioral science research to direct federal policies for better outcomes.<sup>16</sup> Although a few scholars have recognized that modern marketing is often intended to target subconscious biases, they have not addressed the unique situation of alleged “facts” that cannot be verified and instead focused on general marketing, or information presumed to have no factual content based on images, packaging color, or product placement.<sup>17</sup> In contrast, no one has yet addressed the existence and impact of cognitive biases on allegedly factual statements concerning off-label drug

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Reichman & Anthony D. So, *The Case for Public Funding and Public Oversight of Clinical Trials*, ECONOMISTS VOICE (Jan. 2007).

14. See *infra* notes 146–150.

15. There is robust legal scholarship aimed at identifying and addressing unconscious, typically racial biases in areas of policing, prosecuting, judicial decision-making, as well as Eighth Amendment excessive punishment. *E.g.*, Justin D. Levinson, Mark W. Bennett & Koichi Hioki, *Judging Implicit Bias: A National Empirical Study of Judicial Stereotypes*, 69 FLA. L. REV. 63 (2017); Justin D. Levinson & Robert J. Smith, *Systemic Implicit Bias*, 126 YALE L.J. F. 406 (2017); Justin D. Levinson & Danielle Young, *Different Shades of Bias: Skin Tone, Implicit Racial Bias, and Judgments of Ambiguous Evidence*, 112 W. VA. L. REV. 307 (2010); L. Song Richardson, *Police Efficiency and the Fourth Amendment*, 87 IND. L.J. 1143, 1144 (2012) (arguing that the legal test of “reasonable suspicion” is particularly susceptible to implicit bias); Robert J. Smith & Justin D. Levinson, *The Impact of Implicit Racial Bias on the Exercise of Prosecutorial Discretion*, 35 SEATTLE U. L. REV. 795 (2012).

16. Exec. Order No. 13,707, 3 C.F.R. § 13707 (2015).

17. *E.g.*, Micah L. Berman, *Manipulative Marketing and the First Amendment*, 103 GEO. L.J. 497 (2015) (explaining how modern marketing is intended to take advantage of consumer cognitive biases and proposing that “noninformational” marketing such as product placement and color should be granted less First Amendment protection in a manner consistent with the *Central Hudson* test); Ralph S. Brown, Jr., *Advertising and the Public Interest: Legal Protection of Trade Symbols*, 57 YALE L. REV. 1165 (1948) (recognizing the powerful influence of advertising with respect to trademarks); Yoav Hammer, *Expressions Which Preclude Rational Processing: The Case for Regulating Non-Informational Advertisements*, 27 WHITTIER L. REV. 435, 482 (2005); Christine Jolls, *Debiasing Through Law and the First Amendment*, 67 STAN. L. REV. 1411, 1419–36 (2015) (providing empirical data that compelled disclosure of images in three situations may inform consumers contrary to current First Amendment case law that dismiss the ability of images to inform as not factual); see also Tamara R. Piety, *Merchants of Discontent: An Exploration of the Psychology of Advertising, Addiction, and the Implications for Commercial Speech*, 25 SEATTLE U. L. REV. 377, 407–21 (2001) (discussing the psychology of advertising).

promotion whereas companies have for years been aptly relying on the existence of cognitive biases of doctors with their marketing methods.<sup>18</sup>

This Article argues that cognitive biases make doctors susceptible to these alleged facts marketed by companies and that judges, too, have their own cognitive biases that have thus far prevented them from seeing doctors' vulnerability to manipulation. A better understanding of the cognitive biases at issue reveals that the current trend towards greater First Amendment protection of commercial speech for pharmaceutical promotion is unlikely to achieve the traditional goal in First Amendment commercial speech jurisprudence of promoting informed decisions. Moreover, recognizing cognitive biases helps to establish why disclaimers are ineffective, contrary to assumptions in First Amendment case law that such disclaimers are an easy alternative to speech restrictions.<sup>19</sup>

This Article complements existing knowledge and concern about pharmaceutical marketing, as well as broader commercial influences on the practice of medicine. For example, in recent years, scholars and policymakers have expressed concern that doctors may be unduly influenced by pharmaceutical marketing, gifts, industry-funded continuing medical education, and even "opinion leaders" with financial ties to the industry.<sup>20</sup> Some of this concern resulted in the Sunshine Act, which imposed new regulations to minimize financial conflicts of interest between doctors and industry through disclosure of payments and items of certain value, but excluding

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18. E.g., Sunita Sah & Adriane Fugh-Berman, *Physicians Under the Influence: Social Psychology and Industry Marketing Strategies*, 41 J.L. MED. & ETHICS 665 (2013) (noting effective use of social psychology principles by pharmaceutical marketing to which doctors are generally unaware).

19. See *infra* Section II.C.

20. E.g., CARL ELLIOTT, *WHITE COAT, BLACK HAT: ADVENTURES ON THE DARK SIDE OF MEDICINE* (2010); INST. OF MED. OF THE NAT'L ACADS., *CONFLICT OF INTEREST IN MEDICAL RESEARCH, EDUCATION, AND PRACTICE* (Bernard Lo & Marilyn J. Field eds., 2009); see also Rosa Ahn, Alexandra Woodbridge, Ann Abraham, Susan Saba, Deborah Korenstein, Erin Madden, W. John Boscardin & Salomeh Keyhani, *Financial Ties of Principal Investigators and Randomized Controlled Trial Outcomes: Cross Sectional Study*, 356 BRIT. MED. J. 6 (2017) (linking financial conflicts with publication bias); William Fleischman, Shantanu Agrawal, Marissa King, Arjun K. Venkatesh, Harlan M. Krumholz, Douglas McKee, Douglas Brown & Joseph S. Ross, *Association Between Payments from Manufacturers of Pharmaceuticals to Physicians and Regional Prescribing: Cross Sectional Ecological Study*, 354 BRIT. MED. J. 4–5, 7 (2016) (financial conflicts linked to prescribing more expensive drugs); Ashley Wazana, *Physicians and the Pharmaceutical Industry: Is a Gift Ever Just a Gift?*, 283 J. AM. MED. ASS'N. 373 (2000); Charles Ornstein, Mike Tigas & Ryann Grochowski Jones, *Now There's Proof: Docs Who Get Company Cash Tend to Prescribe More Brand-Name Meds*, PROPUBLICA (Mar. 17, 2016, 5:00 AM), <https://www.propublica.org/article/doctors-who-take-company-cash-tend-to-prescribe-more-brand-name-drugs> [<https://perma.cc/E83G-X4VY>] (providing data concerning higher prescriptions of expensive drugs by doctors who received more money as well as the fact that about seventy-five percent of doctors in five common medical specialties received at least one payment in 2014). Even a single meal can influence physician prescribing. E.g., Colette DeJong, Thomas Anguilar, Chien-Wen Tseng, Grace A. Lin, W. John Boscardin & R. Adams Dudley, *Pharmaceutical Industry-Sponsored Meals and Physician Prescribing Patterns for Medicare Beneficiaries*, 176 J. AM. MED. ASS'N 1114 (2016).



others, such as drug samples.<sup>21</sup> However, not only is disclosure an incomplete solution, but also the problem is not solely limited to conflict of interest.<sup>22</sup> After all, even doctors with no financial interest may have biases. This Article complements recognized problems with commercial influences on the practice of medicine but provides a richer explanation than prior scholarship focused on conflicts of interest. Although some issues could be addressed through changes to malpractice law, the focus of this Article is on addressing schemas in First Amendment law.<sup>23</sup>

This Article proceeds in four parts. Part I provides background to understand the key issues. Part I begins with some fundamental concepts of how prescription drugs are developed and approved for sale. In addition, it discusses the unique nature of the prescription drug market, as well as how off-label uses are regulated. Finally, this Part provides an overview of commercial speech law and policy.

Part II provides an introduction to schemas, as well as related cognitive biases as a backdrop to establishing two previously unrecognized schemas that have played a key role in promoting First Amendment fallacies concerning commercial speech. The first schema is that doctors are adequately sophisticated to evaluate pharmaceutical marketing of prescription drugs without being confused or misled (the “sophisticated doctor schema”). The second schema is that more information is

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21. 42 U.S.C. § 1320a-7h (2012). Of course, there are still some outliers that claim conflict of interest is a mere narrative without adequate evidence of negative patient impacts. *E.g.*, D. Barton, T. Stossel & L. Stell, *After 20 Years, Industry Critics, Bury Skeptics, Despite Empirical Vacuum*, 68 INT’L J. CLINICAL PRAC. 666 (2014).

22. See Sandra H. Johnson, *Polluting Medical Judgment? False Assumptions in the Pursuit of False Claims Regarding Off-Label Prescribing*, 9 MINN. J.L. SCI. & TECH. 61, 63–64, 74–76 (2008) (considering conflicts of interest at best a partial accounting of off-label prescribing and that doctors may be simply skeptical about clinical trials); Lisa Rosenbaum, *Understanding Bias – The Case for Careful Study*, 372 NEW ENG. J. MED. 1959, 1960 (2015) (noting that conflict of interest disclosure may be interpreted by viewers as a reason to be more trusting of the information because the disclosure is viewed as a sign of honesty). Moreover, even if disclosures of conflicts of interest provide some value, it seems that disclosures are incomplete since publications seem to rely on authors to voluntarily disclose and do not impose penalties. *E.g.*, Cole Wayant, Erick Turner, Chase Meyer, Philip Sinnett & Matt Vassar, *Financial Conflicts of Interest Among Oncologist Authors of Reports of Clinical Drug Trials*, J. AM. MED. ASS’N ONCOLOGY (2018) (noting that about a third of authors in a sample of cancer trials did not report all payments); see also Charles Ornstein & Katie Thomas, *Top Cancer Researcher Fails to Disclose Corporate Financial Ties in Major Research Journals*, N.Y. TIMES (Sept. 8, 2018), <https://www.nytimes.com/2018/09/08/health/jose-baselga-cancer-memorial-sloan-kettering.html> [<https://perma.cc/LD4Q-ESLU>] (noting a doctor who failed to disclose conflicts of interest in dozens of research articles from a variety of prestigious journals and that most journals do not verify accuracy of information).

23. Although not the focus here, if doctors are less sophisticated in evaluating information than commonly believed, that could suggest changes to medical malpractice laws. Indeed, some have previously suggested that malpractice laws are ineffective in limiting off-label use that could be dangerous. *E.g.*, Philip M. Rosoff & Doriane Lambelet Coleman, *The Case for Legal Regulation of Physicians’ Off-Label Prescribing*, 86 NOTRE DAME L. REV. 649, 666–71 (2011) (suggesting direct regulation of off-label use by limiting prescriptions by doctors for scientifically unsupported uses). However, even if medical malpractice might address some issues, that does not undermine the issue this Article addresses.

always desirable so long as it is not patently false, even if it is potentially misleading (the “more information schema”). Although each of these schemas has some basis in reality, current jurisprudence unduly relies on these schemas to an extent not supported by empirical data. As will be explained, First Amendment case law has thus far assumed that doctors will not be improperly swayed by “facts,” given their sophistication, contrary not only to cognitive bias literature, but growing recognition that doctors are vulnerable to marketing practices as recognized by the enactment of the Sunshine Act. In addition, although First Amendment jurisprudence regarding commercial speech consistently promotes a robust marketplace of ideas, this is contrary to literature about how all individuals incompletely process information, as well as the fact that the pharmaceutical marketplace is an unusual one where there is generally no competing viewpoint.

Part III then considers the implications of the revealed schemas. Importantly, the schemas are not intended to suggest that all off-label marketing is problematic, or that courts should permit an absolute ban on such promotion. This part considers key themes in recent cases and also explains the mismatch between First Amendment policy with the unique and imbalanced marketplace of patented pharmaceuticals.

Part IV provides concrete suggestions for how to combat the revealed schemas. This Part first suggests changes to the law to better align the law with reality, including modifications to commercial speech law relating to off-label use, as well as related suggestions regarding judicial deference to FDA evaluation, and suggestions for future FDA guidance. In addition, this Part suggests reforms that would help address the undue influence of schemas on the practice of medicine generally. Although these strategies would help address the revealed schemas in the context of off-label marketing of drugs, they have broader implications. Some of the proposed changes to the law impact how commercial speech regarding dietary supplements, and especially disclaimers regarding such supplements are evaluated. In addition, some proposed structural changes, such as limiting drug samples would impact all prescription drugs. The implications also extend to broader issues in the field of medicine, such as the need for more independent data, including comparative effectiveness data, as well as questioning the current system of drug development.

## I. BACKGROUND

### *A. Development and Approval of Prescription Drugs*

The development and approval of prescription drugs is important to understand since it impacts both marketing and commercial speech implications. Importantly, although drugs can be considered public goods that benefit society, they are developed by for-profit companies.<sup>24</sup> Since companies have incentives to maximize profits, rather than focus on public health imperatives, regulation is important. Currently, before a new drug can be legally sold, its manufacturer must provide clinical data to the FDA that establishes that the drug is safe and effective for

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24. Given this conflict of interest, some have suggested public funding should promote drug development, and especially clinical trials needed to establish regulatory approval. *E.g.*, Lewis et al., *supra* note 13, at 1.

intended use(s), in what is referred to as premarket approval.<sup>25</sup> The current regulatory scheme was established to avoid public health tragedies of an earlier era where drugs were not regulated at all, or were only regulated for safety, but not efficacy.<sup>26</sup>

When the FDA evaluates whether a proposed new drug has adequate data to establish safety and efficacy, it focuses on the drug's specific "indication(s)," i.e. use(s) for which the manufacturer seeks approval.<sup>27</sup> Basically, the FDA is considering whether a drug's overall benefit versus risks for a *specific* use are satisfactory. After all, a drug is unlikely to be effective and/or safe for all conditions or all individuals.<sup>28</sup> In addition, more risk may be tolerable for some conditions where there are no strong alternatives. The evaluation of drugs based on intended use is important to the FDA's mission in preventing unnecessary public harm.<sup>29</sup> In particular, premarket approval for each intended use is essential to prevent a company from obtaining approval for one use, but then promoting it for a different unapproved use, without adequate scientific basis for the new use.<sup>30</sup> In addition, approval based on specific uses encourages companies to conduct studies to establish whether uses are supported.

While companies must provide substantial clinical data involving multiple phases of human testing to the FDA that indicate the drug is safe and effective for its proposed use(s), FDA approval does not completely guard against problems. First of all, the self-interested company is designing studies to show that its drug is safe and effective. In addition, although the company must submit the results of all clinical studies,<sup>31</sup> the FDA may approve a drug despite equivocal clinical studies<sup>32</sup> since the

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25. 21 U.S.C. § 355 (2012).

26. *Drug Industry Antitrust Act of 1962: Hearing on H.R. 6245 Before the H. Comm. on the Judiciary*, 87th Cong. 67 (1962) ("[T]he physician is bombarded with seductive advertising which fails to tell the truth . . . This often misleads him into prescribing a new drug without adequate warning or information about its possible side effects and, indeed, without any solid clinical evidence that the drug is effective or is even as safe as the advertisers claim."); Henry A. Waxman, *A History of Adverse Drug Experiences: Congress Had Ample Evidence to Support Restrictions on the Promotion of Prescription Drugs*, 58 *FOOD & DRUG L.J.* 299, 301–08 (2003).

27. If approved, the drug "labeling," which includes not just the physical label on a drug, but also anything distributed in connection with the drug, must reflect the approved indication. 21 U.S.C. § 355(d); 21 C.F.R. § 202.1 (2017).

28. *United States v. Rutherford*, 442 U.S. 544, 555 (1979); see STEPHEN J. CECCOLI, *PILL POLITICS: DRUGS AND THE FDA* 165–68 (2004).

29. *What We Do*, FDA, <https://www.fda.gov/aboutfda/whatwedo> [<https://perma.cc/FW7W-SHMR>]; see also FDA Memorandum, *supra* note 6 (noting that the FDA approval based on intended use was developed by Congress in response to public health tragedies).

30. S. REP. No. 87-1744 (1962).

31. 21 C.F.R. § 314.50 (2018).

32. For example, a FOIA request revealed that the six most widely prescribed antidepressants approved between 1987 and 1999 had a combined total of forty-seven efficacy studies, and that more than half of these showed no significant difference between the approved drug and placebo. Irving Kirsch, Thomas J. Moore, Alan Scoboria & Sarah S. Nicholls, *The Emperor's New Drugs: An Analysis of Antidepressant Medication Data Submitted to the U.S. Food and Drug Administration*, PREVENTION & TREATMENT, July 2002, at 3 [hereinafter Kirsch et al., *Analysis of Antidepressant*]; Irving Kirsch, *Antidepressants: The*

legal standard only requires there be “substantial evidence” of the “intended effect,” with the intended effect defined by the company.<sup>33</sup> Importantly, the full results of clinical studies are generally not available to the public including researchers.<sup>34</sup> Even though companies may publish scientific articles relating to approved drugs, they generally selectively publish positive results,<sup>35</sup> and even then, the articles are likely far less detailed than the clinical data available to the FDA.<sup>36</sup> Accordingly, it is not

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*Emperor’s New Drugs?*, HUFFPOST (Nov. 17, 2011), [https://www.huffpost.com/entry/antidepressants-the-emper\\_b\\_442205](https://www.huffpost.com/entry/antidepressants-the-emper_b_442205) [<https://perma.cc/P5RH-9CTZ>]. Moreover, an FDA memo concerning Celexa noted that two controlled efficacy trials showed significant differences between the drug and placebo whereas three others “[f]ailed to provide results confirming the positive findings,” but the FDA nonetheless concluded that “there is clear evidence from more than one adequate and well controlled clinical investigation” that the drug had an antidepressant effect. Kirsch et al., *Analysis of Antidepressant*, *supra*. About a third of drugs are approved based on a single pivotal trial. Nicholas S. Downing, Jenerius A. Aminawung, Nilay D. Shah, Harlan M. Krumholz & Joseph S. Ross, *Clinical Trial Evidence Supporting FDA Approval of Novel Therapeutic Agents 2005-2012*, 311 J. AM. MED. ASS’N 368, 372 (2014).

33. 21 U.S.C. § 355(d)(5)(iv) (2012); *see also* Jonathan J. Darrow, *Pharmaceutical Efficacy: The Illusory Legal Standard*, 70 WASH. & LEE L. REV. 2073 (2013) [hereinafter Darrow, *Pharmaceutical Efficacy*] (criticizing FDA approval standard for lacking any specific level of efficacy and instead simply mandating precise calculation of efficacy). Traditionally, the FDA required at least two clinical trials to suggest a drug is superior to a placebo or conventional treatment. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY: PROVIDING CLINICAL EVIDENCE OF EFFECTIVENESS FOR HUMAN DRUGS AND BIOLOGICAL PRODUCTS 3 (1998). However, there could be other contrary studies. This was definitely true for a number of antidepressants. *See supra* note 32. In addition, as a result of congressional amendments, the FDA can now approve a drug based on positive results from a single trial. 21 U.S.C. § 355(d).

34. The FDA has traditionally considered clinical studies to be a trade secret and fall within an exemption to FOIA requests and courts have concurred. *Judicial Watch, Inc. v. Food & Drug Admin.*, 449 F.3d 141, 149 (D.C. Cir. 2006) (finding that FDA was entitled to withhold some data sought by FOIA request regarding approved drug RU-486 for medical abortion based on the exemption which covers some information contained in NDAs); *Public Information*, 42 Fed. Reg. 3093, 3094 (Jan. 14, 1977) (noting FDA has treated clinical trial data as trade secret since 1938); 21 C.F.R. § 20.85 (1994); *see also* 21 U.S.C. § 355(l) (creating an exemption to FOIA requests in the event of likelihood of substantial competitive harm). However, the FDA position on trade secrecy of clinical data based on 21 U.S.C. § 331(j) has been criticized since clinical data are arguably not a method or process. *E.g.*, Christine D. Galbraith, *Dying to Know: A Demand for Genuine Public Access to Clinical Trial Results Data*, 78 MISS. L.J. 705, 752–42 (2009). In addition, recent laws permit proactive disclosure by the FDA. *E.g.*, 21 U.S.C. § 355(r) (instructing FDA to have website to provide better access to drug safety information for patients and providers and mandating FDA post safety alerts, warning letters, as well as “other material determined appropriate” by the FDA); Amy Kapczynski & Jeanie Kim, *Clinical Trial Transparency: The FDA Should and Can Do More*, 45 J.L. MED. & ETHICS 33, 35 (2017) (noting that FDA should be routinely releasing clinical data, as well as summary results as “other material”). Moreover, even though clinical studies have recently been obtained through FOIA, that was notably a highly time-consuming process. *E.g.*, Kapczynski & Kim, *supra*.

35. *See infra* notes 46, 59–60 and accompanying text (discussing selective publication).

36. *E.g.*, Kapczynski & Kim, *supra* note 34, at 34.

unusual for problems with drugs to be discovered years later by independent researchers who must do their own tests. These researchers may find out that the drug does not work as advertised and sometimes even works *contrary* to how it is advertised.<sup>37</sup> These issues have prompted calls for full disclosure of clinical trial results.<sup>38</sup> Although the FDA does not currently require complete disclosure, it does require companies that seek FDA approval of drugs to publicly register details of

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37. For example, for years, hormone replacement drug therapy was promoted to not only treat menopause, but also to prevent heart disease based on industry-financed data until independent researchers at the NIH discovered that the drugs actually *increased* the risk of heart disease. Nancy Krieger et al., *Hormone Replacement Therapy, Cancer, Controversies, and Women's Health: Historical, Epidemiological, Biological, Clinical, and Advocacy Perspectives*, 59 J. EPIDEMIOLOGY & COMMUNITY HEALTH 740, 740 (2005); see also Lisa A. Ladewski et al., *Dissemination of Information on Potentially Fatal Adverse Drug Reactions for Cancer Drugs from 2000 to 2002: First Results from the Research on Adverse Drug Events and Reports Project*, 21 J. CLINICAL ONCOLOGY 3859 (2003) (discussing serious, including fatal, adverse drug reactions that are only discovered years after FDA approval); Heidi D. Nelson, Miranda Walker, Bernadette Zakher & Jennifer Mitchell, *Menopausal Hormone Therapy for the Primary Prevention of Chronic Conditions: A Systematic Review to Update the U.S. Preventative Services Task Force Recommendations*, 157 ANNALS INTERNAL MED. 104, 109–10 (2012) (systematic review of studies that confirms increased risk of stroke).

38. E.g., Peter Doshi, Tom Jefferson & Chris Del Mar, *The Imperative to Share Clinical Study Reports: Recommendations from the Tamiflu Experience*, PLOS MED., Apr. 2012, at 1–2 (noting that clinical study reports have the same information as journal papers, but more detail); Ben Goldacre, *What the Tamiflu Saga Tells Us About Drug Trials and Big Pharma*, GUARDIAN (Apr. 10, 2014, 2:00 PM), <https://www.theguardian.com/business/2014/apr/10/tamiflu-saga-drug-trials-big-pharma> [<https://perma.cc/4DMV-CG88>]; Katie Thomas, *Breaking the Seal on Drug Research*, N.Y. TIMES (June 29, 2013), <https://www.nytimes.com/2013/06/30/business/breaking-the-seal-on-drug-research.html> [<https://perma.cc/TT5F-8EBH>]. These suggestions were prompted by eventual public disclosure that off-label promotion of Tamiflu to reduce hospital complications was found to be unjustified based on complete data, but only two of ten studies were published and none of published data disclosed negative side effects. Yogendra Gupta, Meenaskshi Meenu & Prafull Mohan, *The Tamiflu Fiasco and Lessons Learnt*, 47 INDIAN J. PHARMACOLOGY 11 (2015); Shannon Brownlee & Jeanne Lenzer, *The Truth About Tamiflu*, ATLANTIC (2009), <https://www.theatlantic.com/magazine/archive/2009/12/the-truth-about-tamiflu/307801> [<https://perma.cc/8GL6-ZGP3>]; see also Jeanne Lenzer, *Conflicting (Conflicted?) Info, Tamiflu and Unquestioning News Reporting*, HEALTHNEWSREVIEW (Feb. 10, 2015), <https://www.healthnewsreview.org/2015/02/conflicting-study-reports-tamiflu-and-unquestioning-news-reporting> [<https://perma.cc/DRS7-XYWB>] (noting that the Centers for Disease Control and Prevention (CDC) promotion of off-label use of Tamiflu was based on a supposedly independent article, but three quarters of the authors received funding).

clinical trials when initiated, as well as provide summary results.<sup>39</sup> However, companies thus far have not fully complied with even these limited disclosures.<sup>40</sup>

### B. Marketing of Prescription Drugs

When a prescription drug is initially approved by the FDA, the *only* source of information regarding the drug is provided by the self-interested drug company.

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39. 42 U.S.C. § 282(j)(2)(C)(ii) (2012) (requiring new clinical trials to submit the trial information to a registry no later than 21 days after first patient is enrolled); 42 C.F.R. § 11.24(a) (2016) (requiring submission of clinical trial registration); 81 Fed. Reg. 64,983 (Sept. 21, 2016) (noting summary data must be submitted in tabular form with key information including primary and secondary outcomes); *see also* Darrow, *Pharmaceutical Efficacy*, *supra* note 33, at 2101 (noting a 2007 change to FDA laws that required all clinical trials to be included as part of Food and Drug Administrative Amendments Act, instead of only serious or life-threatening conditions under 1997 legislation). In addition, the FDA recently announced a pilot program to reveal summary data concerning pivotal trials, although this is on a voluntary basis and still does not reveal all underlying clinical data. Press Release, FDA, FDA Commissioner Scott Gottlieb, M.D., on New Steps FDA Is Taking to Enhance Transparency of Clinical Trial Information to Support Innovation and Scientific Inquiry Related to New Drugs (Jan. 16, 2018), <https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm592566.htm> [<https://perma.cc/6FYV-VP46>]. In contrast, Europe is moving towards proactive publication of clinical trial data, even without a specific request. EUROPEAN MEDS. AGENCY, EUROPEAN MEDICINES AGENCY POLICY ON ACCESS TO DOCUMENTS (RELATED TO MEDICINAL PRODUCTS FOR HUMAN AND VETERINARY USE) (2010); EUROPEAN MEDS. AGENCY, EUROPEAN MEDICINES AGENCY POLICY ON PUBLICATION OF CLINICAL DATA FOR MEDICINAL PRODUCTS FOR HUMAN USE (2014) (permitting online publication of all clinical study reports on a proactive basis since most information is not confidential); *see also* Commission Regulation 726/2004, art. 80, 2004 (EC) (providing basis for Policy 0070); Commission Regulation 536/2014, art. 81, 2014 (EC) (requiring all clinical trials conducted in the European Union to be made available to the public through a publicly available database although with the possibility for some commercially confidential information to be withheld); *see also* Elisa Stefanini, *Publication of Clinical Trials Data: A New Approach to Transparency in the European Legislative Framework*, POINT CARE (2017) (explaining the change in regulations). The EU Regulation is expected to come into effect in 2019. European Commission, *Clinical Trials – Regulation EU No. 536/2014*, [https://ec.europa.eu/health/human-use/clinical-trials/regulation\\_en](https://ec.europa.eu/health/human-use/clinical-trials/regulation_en) [<https://perma.cc/P76T-HECC>].

40. Current reporting is just under sixty percent. *Who's Sharing Their Clinical Trial Results?*, FDAAA TRIALSTRACKER, <http://fdaaa.trialstracker.net/?status%5B%5D=overdue&status%5B%5D=overdue-cancelled&status%5B%5D=reported-late> [<https://perma.cc/G6RD-NSUY>]. Although this is not ideal, it is an improvement. Andrew P. Prayle, Matthew N. Hurley & Alan R. Smyth, *Compliance with Mandatory Reporting of Clinical Trial Results on ClinicalTrials.gov: Cross Sectional Study*, 344 BRIT. MED. J. 3 (2012) (finding seventy-eight percent of trials from 2009 were not reported). In addition, although the FDA could enhance compliance by imposing statutorily permitted penalties of up to \$10,000 a day, it has yet to do so. FDAAA TrialsTracker, *supra* (interactive and constantly updated website noting uncollected fines of over \$300 billion to date); Ben Goldacre, *Health Care's Trick Coin*, N.Y. TIMES (Feb. 1, 2013), <https://www.nytimes.com/2013/02/02/opinion/health-cares-trick-coin.html> [<https://perma.cc/6EVD-367Y>] (noting no fines levied for violation); *see also* 21 U.S.C. § 333(f)(3)(B) (2012) (authorizing penalties of up to \$10,000 a day).

Unlike other consumer goods where there are competing manufacturers in the same class that compare their products to each other, or evaluations by unbiased third parties, that does not happen with these drugs.<sup>41</sup> This is partially because FDA approval is generally based on establishing safety and efficacy, but not on superiority compared to other drugs.<sup>42</sup> So, companies often provide data only comparing their drug to a placebo, known to have no effect, rather than existing treatments.<sup>43</sup> Then, each company that makes and sells one drug in the same class of drugs, such as those that treat heartburn, will market its drug as effective, but generally without any clear indication to doctors or consumers of which drug is better. In addition, in some cases where a company markets its drug as better than a competitor's, the marketing may fail to emphasize key limitations of the comparison, such as the fact that the supporting study compared a weaker dose of the competitor's drug.<sup>44</sup>

In the unique marketplace of prescription drugs, there is initially no unbiased information and advertising looms large in spreading information that may later be determined to be false. Companies can easily present misleading information by only advertising positive information about drugs. In some cases, it is subsequently revealed that companies intentionally concealed known negative information or selectively only presented positive results in marketing<sup>45</sup> and academic

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41. For example, although consumers rely on sources like the magazine *Consumer Reports*, as well as other third-party reviews, nothing similar exists in the more complex area of prescription drugs since reviews are more complex than evaluating goods such as appliances or cars. There are some independent newsletters that provide doctors with information about new drugs. *E.g.*, HEALTH ACTION INT'L, FACT OR FICTION?: WHAT HEALTHCARE PROFESSIONALS NEED TO KNOW ABOUT PHARMACEUTICAL MARKETING IN THE EUROPEAN UNION 52–53 (noting independent sources such as the monthly Prescriber's Letter concerning new treatments as well as "Worst Pills, Best Pills" that provides information on prescription and over-the-counter drugs). However, doctors do not seem to refer to these in studies regarding sources of information.

42. *See* 21 U.S.C. § 355(d) (2012); 21 C.F.R. § 202.1 (2017).

43. *E.g.*, MARCIA ANGELL, THE TRUTH ABOUT DRUG COMPANIES 112 (2004); *see also* CENTER FOR INFORMATION AND STUDY ON CLINICAL RESEARCH PARTICIPATION, WHAT IS A PLACEBO CONTROLLED CLINICAL TRIAL? (explaining placebo controlled clinical trials); Gary T. Chiodo, Susan W. Tolle & Leslie Bevan, *Placebo-Controlled Trials: Good Science or Medical Neglect?*, 172 W.J. MED. 271, 271 (2000) (noting that the gold standard for clinical trials has traditionally been randomized trials comparing experimental treatment with placebo). However, placebos are not typically used in studying treatments regarding serious and life-threatening conditions including cancer. *Clinical Research Versus Medical Treatment*, FOOD & DRUG ADMIN., (Mar. 22, 2018) <https://www.fda.gov/forpatients/clinicaltrials/clinicalvsmedical/default.htm> [<https://perma.cc/7MS7-2H8U>].

44. ANGELL, *supra* note 43, at 78–79. Although this is not helpful to consumers, corporations have incentives to not only promote their bottom line, but to avoid clinical studies that end up helping competitors. *E.g.*, Winslow, *supra* note 11 (discussing Bristol Myers Squibb's failed attempt to establish that its cholesterol-lowering drug compared well to Pfizer's Lipitor in a rare head to head comparison of competing drugs).

45. Sometimes companies instruct sales representatives to not disclose relevant information. *E.g.*, Shannon Hall & Jeanne Lenzer, *The Problem with Medicine: We Don't Know if Most of It Works*, DISCOVER (Feb. 11, 2011), <http://discovermagazine.com/2010/nov/11-the-problem-with-medicine-dont-know-if-most-works> [<https://perma>

publications;<sup>46</sup> there are even reports that companies sometimes threaten independent doctors or scientists who raise issues.<sup>47</sup> Although companies can be

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.cc/A8JG-VBDE] (noting that Pfizer representatives were instructed not to provide relevant study showing that inexpensive generic drugs were equally effective as brand name drugs for reducing heart attacks and actually safer). At other times, sales representatives are instructed to provide messages that are not firmly supported by data. For example, Purdue trained its sales representatives to tell doctors the risk of addiction from OxyContin was less than one percent. This was based on a study involving burn victims treated with opioids that had no bearing on the long term use of opioids to treat chronic pain, and in fact, contradicts many studies showing high incidence of abuse for chronic pain. Art Van Zee, *The Promotion and Marketing of OxyContin: Commercial Triumph, Public Health Tragedy*, 99 AM. J. PUB. HEALTH 221, 223 (2009).

46. A famous example involves the anti-inflammatory drug sold as Vioxx, that was at one point the best-selling drug with over \$2 billion a year in sales—before it was removed from the market after initially suppressed studies revealed that it was associated with an increase in heart attacks and strokes. HOLLY PRESLEY, INSTITUTIONS IN CRISIS: VIOXX AND THE MERCK TEAM EFFORT (2009); see also ELLIOTT, *supra* note 20, at 103 (noting that although company disclosed study showing that Vioxx led to a 500% increase of risk of heart attacks compared to naproxen, Merck stated that naproxen protected the heart); Rita Rubin, *How Did Vioxx Debacle Happen?*, USA TODAY (Oct. 12, 2004, 12:00 AM), [https://usatoday30.usatoday.com/news/health/2004-10-12-vioxx-cover\\_x.htm](https://usatoday30.usatoday.com/news/health/2004-10-12-vioxx-cover_x.htm) [<https://perma.cc/SD2M-7789>]. In some cases, companies have been found to fail to adequately notify the public of known risks. *E.g.*, Press Release, U.S. Senate Comm. on Fin., Grassley, Baucus, Release Committee Report on Avandia, (Feb. 20, 2010), <https://www.finance.senate.gov/release/grassley-baucus-release-committee-report-on-avandia> [<https://perma.cc/T5CQ-WA9A>] (discussing Senate Report concluding that GSK failed to warn patients regarding cardiovascular risks from its drug Avandia and that the company instead improperly intimidated independent doctors to not discuss problems). Along somewhat similar lines, companies sometimes financially support entities that appear independent to the public, but essentially advocate the corporate position; these could be seemingly independent associations, as well as patient advocacy groups. *E.g.*, Celine Grounder, *Who Is Responsible for the Pain-Pill Epidemic?*, NEW YORKER (Nov. 8, 2013), <https://www.newyorker.com/business/currency/who-is-responsible-for-the-pain-pill-epidemic> [<https://perma.cc/LZK9-TN9A>] (noting the role of the Joint Commission, which controls accreditation of health facilities and was funded by companies to penalize physicians for undertreatment of pain that helped to encourage more use of opioids); Charles Ornstein & Tracy Weber, *American Pain Foundation Shuts Down as Senators Launch Investigation of Prescription Narcotics*, PROPUBLICA (May 8, 2012, 8:57 PM), <https://www.propublica.org/article/senate-panel-investigates-drug-company-ties-to-pain-groups> [<https://perma.cc/R4BK-4HV5>] (noting financial ties between the now defunct American Pain Foundation and the industry); Charles Ornstein & Tracy Weber, *The Champion of Painkillers*, PROPUBLICA (Dec. 23, 2011, 9:15 AM), <https://www.propublica.org/article/the-champion-of-painkillers> [<https://perma.cc/EA9V-Q5UT>] (noting American Pain Society's role in encouraging aggressive treatment of pain, including use of narcotics).

47. *E.g.*, ELLIOTT, *supra* note 20, at 103–04 (noting Merck attempts to neutralize and discredit those that raised concerns regarding Vioxx and heart disease included threatening withdrawal of funding to researcher's university); Gardiner Harris, *Research Ties Diabetes Drug to Heart Woes*, N.Y. TIMES (Feb. 19, 2010), <https://www.nytimes.com/2010/02/20/health/policy/20avandia.html> [<https://perma.cc/4PEU-SVF6>] (noting that GlaxoSmithKline intimidated independent doctors and investigators with potential legal



sanctioned,<sup>48</sup> the reality is that before problems are discovered, public health may be at risk for a number of years.<sup>49</sup> Moreover, public health may suffer even after independent scientists debunk pharmaceutical claims; a pivotal example is the opioid epidemic that resulted from aggressive industry marketing that included affirmatively false information, such as the assertion that opioids were not addictive, which resulted in a settlement of criminal charges in 2007, as well as more recent litigation for continuing misrepresentation.<sup>50</sup>

Companies seem well aware of the relevance and impact of their advertising since they spend substantial resources advertising not only to consumers in the United

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action for suggesting heart risks with its drug Avandia even though the company was aware of risks, yet continued to market the drug aggressively).

48. For example, Paxil was sued for fraud for concealing negative information about Paxil, that included four negative clinical trials and only one positive one. Complaint, United States v. GlaxoSmithKline (D. Mass. Oct. 26, 2011) (No. 11-10398-RWZ) (suit for false claims act).

49. For example, Paxil was sued for fraud for concealing negative information about Paxil, that included four negative clinical trials and only one positive one. Complaint, United States v. GlaxoSmithKline (D. Mass. Oct. 26, 2011) (No. 11-10398-RWZ) (suit for false claims act). Gupta, *supra* note 38, at 11, 13 (noting that serious adverse events were reported after approval of Tamiflu that were not in the selectively published articles). Indeed, one scholar has suggested that newly approved FDA drugs are de facto tested on the general public since it is impossible for “clinical trials to detect rare adverse events.” Jonathan J. Darrow, *Crowdsourcing Clinical Trials*, 98 MINN. L. REV. 805, 805 (2014).

50. United States v. Purdue Frederick Co., 495 F. Supp. 2d 569 (W.D. Va. 2007); Complaint, Oregon v. Purdue (Or. Cir. Ct., Sept. 18, 2018), [https://www.doj.state.or.us/wp-content/uploads/2018/09/State\\_v\\_Purdue\\_Complaint.pdf](https://www.doj.state.or.us/wp-content/uploads/2018/09/State_v_Purdue_Complaint.pdf) [<https://perma.cc/ZK3H-WGND>]; Barry Meier, *In Guilty Plea, OxyContin Maker to Pay \$600 Million*, N.Y. TIMES (May 10, 2007), <https://www.nytimes.com/2007/05/10/business/11drug-web.html> [<https://perma.cc/D7DH-585S>]; Barry Meier, *Origins of an Epidemic: Purdue Pharma Knew its Opioids Were Widely Used*, N.Y. TIMES (May 29, 2018), <https://www.nytimes.com/2018/05/29/health/purdue-opioids-oxycotin.html> [<https://perma.cc/RK2V-GB4M>]; Joanna Walters, *Oxycontin Maker Expected ‘A Blizzard of Prescriptions’ Following Drug’s Launch*, GUARDIAN (Jan 16, 2019, 1:00 PM), <https://www.theguardian.com/us-news/2019/jan/15/oxycotin-purdue-pharma-massachusetts-opioid-crisis> [<https://perma.cc/94F7-238U>]; Katie Zezima & Lenny Bernstein, *Hammer on the Abusers’: Mass. Attorney General Alleges Purdue Pharma Tried to Shift Blame for Opioid Addiction*, WASH. POST (Jan 15, 2019), [https://www.washingtonpost.com/national/hammer-on-the-abusers-mass-attorney-general-alleges-purdue-pharma-tried-to-shift-blame-for-opioid-addiction/2019/01/15/4af25c4c-190c-11e9-88fe-f9f77a3bcb6c\\_story.html?utm\\_term=.40c054446211](https://www.washingtonpost.com/national/hammer-on-the-abusers-mass-attorney-general-alleges-purdue-pharma-tried-to-shift-blame-for-opioid-addiction/2019/01/15/4af25c4c-190c-11e9-88fe-f9f77a3bcb6c_story.html?utm_term=.40c054446211) [<https://perma.cc/3RNP-ZM92>].

States,<sup>51</sup> but also especially to doctors.<sup>52</sup> Most money is spent on “detailing,” which refers to work done by individual sales representatives who visit doctors to personally inform them of new drugs with presentations and brochures, as well as provide samples.<sup>53</sup> Unsurprisingly, this information has been found to be incomplete and misleading.<sup>54</sup> Although doctors generally recognize that detailing is likely biased, they may still rely on it because it is convenient.<sup>55</sup> Along somewhat similar lines, companies have developed relationships with doctors who are perceived as key opinion leaders to influence peers and even provide specific presentation slides for

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51. The United States is one of two countries permitting companies to advertise drugs directly to consumers (the other being New Zealand); in both cases, such advertising is of relatively recent vintage. Sandra Coney, *Direct-to-Consumer Advertising of Prescription Pharmaceuticals: A Consumer Perspective from New Zealand*, 21 J. PUB. POL’Y & MARKETING 213, 213–14 (2002) (explaining that New Zealand laws were not explicitly written to cover advertising, but the industry exploited them in the late 1980s and despite subsequent proposal to ban such advertising, it has remained). Spending on such ads has since grown substantially. Avinandan Mukherjee, Yam Limbu & Isaac Wanasika, *A Review of Research on Direct-to-Consumer Advertising of Prescription Drugs: Directions for Future Research*, 7 INT’L J. PHARMACEUTICAL & HEALTHCARE MARKETING 226, 226–27 (2013) (noting a 330% increase between 1996 and 2005).

52. See Lisa M. Schwartz & Steven Woloshin, *Medical Marketing in the United States, 1997-2016*, 32 J. AM. MED. ASS’N 80, 82, 87 (2019) (finding that marketing to medical professionals accounted for the highest proportion of spending during the time studied); *Persuading the Prescribers: Pharmaceutical Industry Marketing and Its Influence on Physicians and Patients*, PEW (Nov. 11, 2013), <https://www.pewtrusts.org/en/research-and-analysis/fact-sheets/2013/11/11/persuading-the-prescribers-pharmaceutical-industry-marketing-and-its-influence-on-physicians-and-patients> [<https://perma.cc/75CU-EJBD>] (noting that the industry spent \$27 billion in 2012, including more than \$24 billion marketing to doctors alone); Nicole Van Groningen, *Big Pharma Gives Your Doctor Gifts. Then Your Doctor Gives You Big Pharma’s Drugs*, WASH. POST (June 13, 2017), [https://www.washingtonpost.com/opinions/big-pharma-gives-your-doctor-gifts-then-your-doctor-gives-you-big-pharmas-drugs/2017/06/13/5bc0b550-5045-11e7-b064-828ba60fbb98\\_story.html?noredirect=on&utm\\_term=.b80b1f9ee8fd](https://www.washingtonpost.com/opinions/big-pharma-gives-your-doctor-gifts-then-your-doctor-gives-you-big-pharmas-drugs/2017/06/13/5bc0b550-5045-11e7-b064-828ba60fbb98_story.html?noredirect=on&utm_term=.b80b1f9ee8fd) [<https://perma.cc/XT7V-URWX>] (noting that the industry spent \$24 billion marketing to health care professionals in 2012, which is eight times the amount spent advertising to consumers). It is estimated that the industry spends \$8000–\$13,000 per year on an individual doctor. See Wazana, *supra* note 20, at 373.

53. Marc-André Gagnon & Joel Lexchin, *The Cost of Pushing Pills: A New Estimate of Pharmaceutical Promotion Expenditures in the United States*, PLOS MED., Jan. 2008, at 29–31 (finding that detailing and samples constituted the majority of marketing expenditures); see also Schwartz & Woloshin, *supra* note 52, at 84, 86 (finding the cost of detailing to doctors far exceeded medical journal advertising and that companies spent even more on the cost of samples).

54. E.g., Smita Mali, Sujata Dudhgaonkar & N. Bachewar, *Evaluation of Rationality of Promotional Drug Literature Using World Health Organization Guidelines*, 42 INDIAN J. PHARMACOLOGY 267 (2010). John Oliver has exposed this problem to the public at large. *Marketing to Doctors: Last Week Tonight with John Oliver (HBO)*, YOUTUBE (Feb. 8, 2015), <https://www.youtube.com/watch?v=YQZ2UeOTO3I> [<https://perma.cc/85EE-RJ88>].

55. See HEALTH ACTION INT’L, *supra* note 41, at 13 (noting that health professionals are short on time and thus may be vulnerable to marketing); see also *infra* note 168 and accompanying text (noting that some doctors’ belief in the value of marketing is so strong that they joined a lawsuit against the FDA to permit more marketing).

such opinion leaders.<sup>56</sup> In addition, companies finance scientific studies to be published in peer reviewed journals to support their drugs.<sup>57</sup> Although peer review journals are often presumed to be unbiased, especially by courts,<sup>58</sup> in recent years, studies have found problems with such articles since there is a general publication bias towards positive results, with some results incapable of reproduction.<sup>59</sup> Moreover, studies published by self-interested companies are four times more likely to have favorable outcomes.<sup>60</sup> This is not surprising since the industry has no interest in publishing unfavorable data; so, even though the FDA has all the data, the public knowledge is incomplete. There are some notable instances of public harm during the period after drug approval when independent scientists conduct their own studies without access to original data.<sup>61</sup> In addition, the incomplete public knowledge from

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56. *E.g.*, Sergio Sismondo, *Key Opinion Leaders and the Corruption of Medical Knowledge: What the Sunshine Act Will and Won't Cast Light on*, 41 J.L. MED. & ETHICS 635 (2013). Of course, after the Sunshine Act, payments to physicians need to be disclosed, which might limit payments. However, this nonetheless is an example of how companies are invested in utilizing all possible avenues of influencing doctors, including methods that other doctors may not perceive as marketing.

57. *E.g.*, ELLIOTT, *supra* note 20, at 28–39 (discussing the ghost writing of articles); Joel Lexchin, *Those Who Have the Gold Make the Evidence: How the Pharmaceutical Industry Biases the Outcomes of Clinical Trials of Medications*, 18 SCI. & ENGINEERING ETHICS 247 (2011). Journals have their own self-interest to consider when publishing articles from the industry that sponsors lucrative ads. *See* ELLIOTT, *supra* note 20, at 39 (noting that in 2004 medical journals generated twice as much from advertising revenue as from subscriptions); Kamran Abbasi & Richard Smith, *No More Free Lunches*, 326 BRIT. MED. J. 1155 (2003) (“[T]he stark reality is that without pharmaceutical sponsorship many journals would not survive.”). Moreover, companies that publish articles will also pay hefty fees for reprints of the articles to then distribute to doctors. ELLIOTT, *supra* note 20, at 41.

58. *E.g.*, *Wash. Legal Found. v. Friedman*, 13 F. Supp. 2d 51, 67 (D.D.C. 1998) (noting that the “FDA exaggerates its overall place in the universe” in suggesting that FDA review was necessary to ensure accuracy of data in peer review publications that companies wanted to promote).

59. *E.g.*, John P. A. Ioannidis, *Why Most Published Research Findings Are False*, PLOS MED., Aug. 2015, at 0696, 0697; SILAS BOYE NISSEN, TALI MAGIDSON, KEVIN GROSS & CARL T. BERGSTROM, *eLIFE, PUBLICATION BIAS AND THE CANONIZATION OF FALSE FACTS* 1, 13 (2016).

60. Joel Lexchin, Lisa A. Bero, Benjamin Djulbegovic & Otavio Clark, *Pharmaceutical Industry Sponsorship and Research Outcome and Quality: Systematic Review*, 326 BRIT. MED. J. 1167 (2003); Richard Smith, *Medical Journals Are an Extension of the Marketing Arm of Pharmaceutical Companies*, PLOS MED., May 2005, at 364; *see also* Donald W. Light, Joel Lexchin & Jonathan J. Darrow, *Institutional Corruption of Pharmaceuticals and the Myth of Safe and Effective Drugs*, 14 J.L. MED. & ETHICS 590, 595 (2013) (noting that positive results can be published twice). This can be done “by asking the ‘right’ questions,” such as comparing the drug with a treatment known to be inferior, or low doses of competitor drugs, as well as publishing the same results multiple times. Smith, *supra*, at 365; *see also* Christopher T. Robertson, *The Money Blind: How to Stop Industry Bias in Biomedical Science, Without Violating the First Amendment*, 37 AM. J.L. & MED. 358, 370–71 (2013).

61. Vioxx is an excellent example of this problem since a published article failed to disclose all data and misrepresented heart risks. Harlan Krumholz et al., *What Have We Learnt from Vioxx?*, 334 BRIT. MED. J. 120, 121 (2007).

published literature is further complicated by the fact that some seemingly independent articles may actually be ghost written by the industry.<sup>62</sup>

Studies repeatedly show that pharmaceutical promotion efforts do influence which drugs doctors prescribe. Some studies indicate that doctors who rely more on marketing information tend to prescribe more.<sup>63</sup> Meetings with pharmaceutical representatives impact prescriptions, as well as doctor requests for drugs to be added to formularies, even when not superior to existing drugs.<sup>64</sup> Pharmaceutical marketing can be highly effective at driving demand for drugs, even when those drugs are not superior to existing drugs.<sup>65</sup> The effectiveness of marketing to persuade doctors is

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62. ELLIOTT, *supra* note 20, at 28–39 (discussing ghost-writing articles).

63. *E.g.*, Roberto Cardarelli, John C. Licciardone & Lockwood G. Taylor, *A Cross-Sectional Evidence-Based Review of Pharmaceutical Promotional Marketing Brochures and Their Underlying Studies: Is What They Tell Us Important and True?*, BMC FAM. PRAC., Mar. 2006, at 1, 2; T. Shawn Caudill, Nicole Lurie & Eugene C. Rich., *The Influence of Pharmaceutical Industry Advertising on Physician Prescribing*, 22 J. DRUG ISSUES 331 (2012).

64. Wazana *supra* note 20, at 375 (noting multiple studies showing that meeting with pharmaceutical representatives was associated with increased prescriptions and formulary requests and that these drugs generally presented no therapeutic advantage); *see also* Wash. Legal Found. v. Friedman, 13 F. Supp. 2d 51, 63–64 (D.D.C. 1998) (noting substantial evidence that meeting with representatives increased prescription sales, such that manufacturers would want to disseminate information even though the court ultimately found it impermissible for the FDA to limit information from representatives). The impact of detailing is also underscored by the fact that when detailing is limited, prescriptions fall. Ian Larkin, Desmond Ang, Jerry Avorn & Aaron S. Kesselheim, *Restrictions on Pharmaceutical Detailing Reduced Off-Label Prescribing of Antidepressants and Antipsychotics in Children*, 33 HEALTH AFF. 1014, 1020–21 (2014) [hereinafter Larkin et al., *Restrictions*] (finding that after strict detailing policies, there was a reduction in market share of more than one-third of drugs detailed and approved for use in children and even for uses unapproved in children, even though these should theoretically never have been promoted); *see also* Ian Larkin et al., *Association Between Academic Medical Center Pharmaceutical Detailing Policies and Physician Prescribing*, 317 J. AM. MED. ASS'N 1785 (2017) [hereinafter Larkin et al., *Physician Prescribing*] (finding association between limiting representatives and change in prescribing).

65. *E.g.*, Cardarelli et al., *supra* note 63, at 2 (noting that marketing of expensive new drugs using calcium channel blockers resulted in the new drugs commanding a greater market share than older and equally effective drugs); Hall & Lenzer, *supra* note 45 (quoting Dr. Hoffman, a professor of emergency medicine at the University of Southern California, who says that repeatedly “[s]ome expensive new drug becomes a blockbuster best seller following extensive marketing, even though the best one might be able to say about it is that it seems statistically ‘non-inferior’ to an older, cheaper drug”). Moreover, this can lead to public health problems, such as with Vioxx, which was not only not better than prior drugs, but actually *less* safe, as well as OxyContin, which provided no advantage over existing opioids, but aggressive promotion has promoted an opioid addiction crisis. Van Zee, *supra* note 45, at 221–24 (noting studies that indicate the drug’s only improvement is reduced dosing, but that marketing of false information, together with generous bonuses to representatives for such marketing, resulted in a nearly tenfold increase of prescriptions for non-cancer pain relief, as well as addiction). Indeed, OxyContin was the most prescribed brand name opioid in 2001 for moderate to severe pain, even though it had not been shown to be superior to other opioids. *Id.* at 225.

not surprising since companies have relied heavily on methods known in marketing literature to be persuasive.<sup>66</sup> Moreover, companies also indirectly influence doctors by marketing directly to consumers. Studies have shown that some doctors feel pressure to prescribe a specific drug requested by a consumer, even when a doctor may not be personally persuaded that it is a superior treatment.<sup>67</sup> Some policies intended to limit pharmaceutical company interaction with physicians to decrease conflicts of interest have resulted in changes to some prescription behavior.<sup>68</sup>

### C. FDA Regulation of Off-Label Uses

An important subset of pharmaceutical marketing involves the extent to which companies are permitted to regulate so-called “off-label” uses of drugs that the FDA has approved. This Section briefly explains what off-label use is, and then explains the current FDA position on regulation of the marketing of such uses.

The first question is what constitutes an “off-label” use. As previously discussed, the FDA approves a specific drug not for any purpose, but only for intended purpose(s) that a company requests. So, when a company requests FDA approval of a drug, it focuses its clinical tests on the intended purpose(s) it wishes to establish as safe and effective, rather than all possible purposes. Notably, although FDA approval is based on particular intended use(s), once approved, a drug may be prescribed by a

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66. E. E. Roughead, K. J. Harvey & A. L. Gilbert, *Commercial Detailing Techniques Used by Pharmaceutical Representatives to Influence Prescribing*, 28 AUSTL. & N.Z. J. MED. 306, 307 (1998) (techniques include reciprocity for gifts, friendship, social validation, appeal to authority, and scarcity); Allen F. Shaughnessy, David C. Slawson & Joshua H. Bennett, *Separating the Wheat from the Chaff: Identifying Fallacies in Pharmaceutical Promotion*, 9 J. GEN. INTERNAL MED. 563 (1994) (noting that although information on its own almost never persuades, all advertising, including advertisement of drugs, is successful by appealing to emotions and vulnerabilities).

67. *E.g.*, Barbara Mintzes, Morris L. Barer, Richard L. Kravitz, Ken Bassett, Joel Lexchin, Arminée Kazanjian, Robert G. Evans, Richard Pan & Stephen A. Marion, *How Does Direct-to-Consumer Advertising (DTCA) Affect Prescribing? A Survey in Primary Care Environments with and Without Legal DTCA*, 169 CANADIAN MED. ASS'N J. 405, 408, 411 (2003) (finding that advertising leads to patient requests for drugs and that doctors in roughly half of cases prescribed a drug that was “unlikely” or only “possibly” relevant); Joel S. Weissman, David Blumenthal, Alvin J. Silk, Michael Newman, Kinga Zapert, Robert Leitman & Sandra Feibelmann, *Physicians Report on Patient Encounters Involving Direct-to-Consumer Advertising*, HEALTH AFF. (WEB EXCLUSIVE) 219, 225 (2004) (finding that thirty-nine percent of doctors prescribed advertised drugs, with less than half believing the prescribed drug was the most effective drug for the patient). Some have suggested that doctors yield to patient requests to avoid disappointment, as well as switching physicians. *E.g.*, Robert A. Bell, Michael S. Wilkes & Richard L. Kravitz, *Advertisement-Induced Prescription Drug Requests: Patients' Anticipated Reactions to a Physician Who Refuses*, 48 J. FAM. PRAC. 446 (1999).

68. Larkin et al., *Physician Prescribing*, *supra* note 64, at 1786, 1793 (2017) (providing an evaluation of U.S. academic medical centers in five states with largest number of academically affiliated physicians found eight of eleven institutions with policies regulating gifts and representative access to have statistically significant results, as well as statistically significant changes in market share for six of eight drug classes).

doctor for *any* purpose, including uses not approved by the FDA.<sup>69</sup> In other words, when a doctor prescribes an approved drug for a different purpose or use, it is considered “off-label.”

At first glance, it may seem inefficient for the FDA to only evaluate a drug based on one, or even a few limited, intended purposes. However, the FDA regulatory system involves a delicate balance. The FDA wants to protect public health and also wants the regulatory system to incentivize companies to develop and submit data to support specific uses. So, for example, a company that obtains approval for one initial use of a drug can later request approval for additional uses—if it provides data establishing these new uses as safe and effective.<sup>70</sup> However, since FDA jurisdiction covers drugs, but not the practice of medicine, the FDA does not bar doctors from prescribing drugs for off-label use.<sup>71</sup>

The FDA did not initially set out to regulate off-label uses, or marketing of such uses. Rather, it only considered regulating off-label use after a specific off-label use touted in a journal article led to serious concern that ultimately prompted congressional pressure for the FDA to rigorously regulate off-label use.<sup>72</sup> The FDA initially proposed direct regulation of off-label use, but after opposition from doctors, the FDA asserted it would not limit medical treatment and nixed a proposal to bar shipments of drugs for off-label use.<sup>73</sup> Since then, the FDA has developed its current position that focuses on limiting dissemination of information by self-interested companies about possible uses that it has not evaluated. This focus arises out of concern that such communications, although potentially helpful, might not fairly represent reliable scientific information because of a potential to mislead, given that the FDA has not had any opportunity to verify whether the communication is scientifically supported.

The FDA currently regulates off-label use of drugs through a complex and indirect scheme focused on companies;<sup>74</sup> this regulation incentivizes companies to conduct scientific studies to establish whether new uses are supported.<sup>75</sup> There is no express legal prohibition of off-label promotion under the existing statute.<sup>76</sup> Rather,

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69. *E.g.*, *United States v. Caronia*, 703 F.3d 149, 153 (2d Cir. 2012).

70. This is consistent with the fact that the FDA evaluates whether a drug is safe and effective for a stated indication. *See supra* Section I.A. In addition, companies can and do often obtain approvals for many different uses of a drug. For example, Abbvie has obtained many approvals for different uses of its blockbuster drug Humira. *10th New Indication for Humira Approved by FDA*, PHARMALETTER (Jan. 7, 2016) <https://www.thepharmaletter.com/article/10th-new-indication-for-humira-approved-by-fda> [<https://perma.cc/CLG7-VUC6>].

71. 21 U.S.C. § 396 (2012).

72. *Klasmeier & Redish*, *supra* note 5, at 321–22.

73. *Id.* at 322–23.

74. *See* *Amarin Pharma, Inc. v. FDA*, 119 F. Supp. 3d 196, 205 (S.D.N.Y. 2015); *see also* Nathan Cortez, *The Statutory Case Against Off-Label Promotion*, 83 U. CHI. L. REV. ONLINE 124 (2016) (explaining why FDA regulation of off-label promotion is justified).

75. FDA Memorandum, *supra* note 6.

76. *See* *United States v. Caronia*, 703 F.3d 149, 154 (2d Cir. 2012) (“The FDCA and its accompanying regulations do not expressly prohibit the ‘promotion’ or ‘marketing’ of drugs for off-label use.”). However, labeling that suggests an unapproved use may cause a drug to be “new,” for that use, such that a company could be liable of introducing a new drug into interstate commerce without approval. 21 C.F.R. § 202.1(e)(4)(i)(a) (2017).

companies, and their representatives, may be subject to criminal liability if they introduce, or conspire to introduce, a “misbranded” drug into interstate commerce.<sup>77</sup> What constitutes a “misbranded” drug, in turn, includes if its “labeling” is inadequate for “intended use.”<sup>78</sup> Labeling is defined to include not just the actual label on a drug, but also accompanying documents, even if separately distributed.<sup>79</sup> Intended use can be established by advertising as well as oral or written statements by representatives of a company.<sup>80</sup> Given the complex web of statutory provisions involved, as well as First Amendment challenges, the FDA has issued a series of guidance documents over the years concerning what actions would immunize a company from prosecution for misbranding.<sup>81</sup>

Misbranding is a serious issue for companies not only because it may result in criminal liability. In particular, a criminal conviction against a company due to misbranding can result in the complete exclusion of all of its drugs from participation in federal health care programs, such as Medicare and Medicaid, which serve as significant sources of revenue for most pharmaceutical companies.<sup>82</sup> In addition, a company that promotes a drug for off-label use may face substantial fines under the False Claims Act based on the theory that marketing of off-label use caused false claims to be submitted for government programs, such as Medicare, knowing that such claims cannot be properly reimbursed.<sup>83</sup>

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77. 21 U.S.C. § 331(a) (2012).

78. 21 U.S.C. § 352 (a), (f) (2012).

79. 21 U.S.C. § 321(m) (2012); 21 C.F.R. § 202.1(l)(2) (2017).

80. 21 C.F.R. § 201.128 (2017). In addition, a recent revision added a “totality of evidence” requirement. 82 Fed. Reg. 2193 (Jan. 9, 2017) (revising the standard of intended use for 21 C.F.R. § 201).

81. Thus far, guidance documents have increasingly liberalized what companies may do, especially in light of recent commercial speech cases. Indeed, the most recent guidance documents issued in June 2018 are a further expansion of the 2017 proposed guidelines. Compare U.S. DEP’T OF HEALTH & HUMAN SERVS., FOOD & DRUG ADMIN., CTR. FOR DRUG EVALUATION & RESEARCH, CTR. FOR BIOLOGICS EVALUATION & RESEARCH, CTR. FOR DEVICES & RADIOLOGICAL HEALTH & OFFICE OF THE COMM’R, DRUG AND DEVICE MANUFACTURER COMMUNICATIONS WITH PAYORS, FORMULARY COMMITTEES, AND SIMILAR ENTITIES—QUESTION AND ANSWERS: GUIDANCE FOR INDUSTRY AND REVIEW STAFF (2018), with U.S. DEP’T OF HEALTH & HUMAN SERVS., FOOD & DRUG ADMIN., CTR. FOR DRUG EVALUATION & RESEARCH, CTR. FOR BIOLOGICS EVALUATION & RESEARCH, CTR. FOR DEVICES & RADIOLOGICAL HEALTH & OFFICE OF THE COMM’R, DRUG AND DEVICE MANUFACTURER COMMUNICATIONS WITH PAYORS, FORMULARY COMMITTEES, AND SIMILAR ENTITIES—QUESTION AND ANSWERS: GUIDANCE FOR INDUSTRY AND REVIEW STAFF (2017); see also ROPES & GRAY, FDA ISSUES FINAL GUIDANCE DOCUMENTS RELATING TO MEDICAL PRODUCT MANUFACTURER COMMUNICATIONS (2018) (referring to guidance documents as providing more flexibility to manufacturers, as well as noting specific changes such as expanding the safe harbor to include new uses in addition to investigational products).

82. See 42 U.S.C. § 1320a-7b(f) (2012); see also Katrice Bridges Copeland, *Enforcing Integrity*, 87 IND. L.J. 1033 (2012).

83. 18 U.S.C. § 287 (2012); 31 U.S.C. § 3729 (2012); see also Joan H. Krause, *Truth, Falsity, and Fraud: Off-Label Drug Settlements and the Future of the Civil False Claims Act*, 71 FOOD & DRUG L.J. 401 (2016).

Despite the serious legal implications of off-label promotion, companies may be acting rationally in accepting these risks and promoting off-label drugs. Companies seem to consider possible fines simply as part of the cost of doing business given that virtually all major pharmaceutical companies have settled for eye-popping amounts yet continue to promote drugs off-label.<sup>84</sup> For example, Pfizer paid \$2.3 billion for illegally marketing the painkiller sold as Bextra, which was a record amount in 2009, yet it constituted less than three weeks of sales.<sup>85</sup> In addition, although the financial implications of being barred from Medicare and Medicaid is a substantial threat, because the federal government has never barred a company and instead has settled suits for a fraction of possible profits, it has not been a serious one.<sup>86</sup> Companies also have an incentive to promote drugs for all possible uses—even if not legally permitted—due to the fact that such drugs are oftentimes patented but with a relatively short window for companies to recoup profits. In particular, a patent on a drug permits a company to exclude all others from making the identical drug during the effective patent term, which is roughly ten years after FDA approval.<sup>87</sup> Moreover, since not all drugs investigated by a company make it to the marketplace, companies have an incentive to maximize profits for FDA-approved patented drugs before the patent expires and other companies can make identical versions (i.e., low-cost generics) which can substantially undermine profits. Although a company could seek approval for a use currently not approved, that takes time and money, and may not be considered worthwhile if the patent term has expired or is soon to expire.

Although off-label use of drugs is not a new phenomenon, and in some situations is reasonable,<sup>88</sup> recent expansion of commercial speech to permit greater promotion

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84. See, e.g., SAMMY ALMASHAT, SIDNEY M. WOLFE & MICHAEL CAROME, TWENTY-FIVE YEARS OF PHARMACEUTICAL INDUSTRY CRIMINAL AND CIVIL PENALTIES: 1991 THROUGH 2015 (2016), [https://www.citizen.org/sites/default/files/2311\\_0.pdf](https://www.citizen.org/sites/default/files/2311_0.pdf) [<http://perma.cc/3B25-73BY>]; Lena Groeger, *Big Pharma's Big Fines*, PROPUBLICA (Feb. 24, 2014), <http://projects.propublica.org/graphics/bigpharma> [<https://perma.cc/K5X4-T6HS>]; see also Aaron S. Kesslehim, Devan Darby, David M. Studdert, Robert Glynn, Raisa Levin & Jerry Avorn, *False Claims Act Prosecution Did Not Deter Off-Label Drug Use in the Case of Neurontin*, 30 HEALTH AFF. 2318 (2011).

85. Gardiner Harris, *Pfizer Pays \$2.3 Billion to Settle Marketing Case*, N.Y. TIMES (Sept. 2, 2009), <http://www.nytimes.com/2009/09/03/business/03health.html> [<https://perma.cc/26NK-AUC5>].

86. E.g., Copeland, *supra* note 82, at 1035.

87. 35 U.S.C. § 271 (2012). Although the patent term is longer than this, since a patented drug can't be sold without FDA approval, which usually comes several years after the patent is granted, the commercially effective term is shorter. Henry G. Grabowski & John M. Vernon, *Effective Patent Life in Pharmaceuticals*, 19 INT'L J. TECH. MGMT. 98, 109 (2000) (finding mean of 11.7 years for analyzing drugs approved between 1990 and 1995). However, recent studies suggest that due to patent protection of multiple *aspects* of a marketed drug, the combined effective patent term could be longer. Amy Kapczynski, Chan Park & Bhaven Sampat, *Polymorphs and Prodrugs and Salts (Oh My!): An Empirical Analysis of "Secondary" Pharmaceutical Patents*, PLOS ONE, Dec. 2012, at 6 (finding secondary patents can add four to eleven additional years of patent term).

88. E.g., *Amarin Pharma, Inc. v. FDA*, 119 F. Supp. 3d 196, 201–03 (S.D.N.Y. 2015) (noting that off-label uses are widely recognized, including by the FDA itself). This may be true where there is no FDA approved treatment for a condition. See FDA Memorandum, *supra*



of off-label uses creates a public health concern.<sup>89</sup> Studies indicate that about three quarters of off-label uses have *little or no scientific evidence* to support them.<sup>90</sup> This can be problematic since even before the expansion of commercial speech for off-label marketing, one study suggested that approximately twenty percent of prescriptions were for off-label uses.<sup>91</sup> Similarly, before the commercial speech expansion, there have been documented instances of death or serious injuries including heart problems<sup>92</sup> and strokes,<sup>93</sup> based on off-label marketing.<sup>94</sup> Fatal reactions from off-label uses of drugs may even result in the FDA adding warnings to the packaging even though the off-label use is not officially FDA regulated.<sup>95</sup>

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note 6. Similarly, since most drugs are tested on adults, rather than children, off-label usage is also important in that context. Alicia T. F. Bazzano, Rita Mangione-Smith, Matthias Schonlau, Marika J. Suttorp & Robert H. Brook, *Off-Label Prescribing to Children in the United States Outpatient Setting*, 9 ACAD. PEDIATRICS 81 (2009); Aaron S. Kesselheim & Jerry Avorn, *Pharmaceutical Promotion of Physicians and First Amendment Rights*, 358 NEW ENG. J. MED. 1727, 1730 (2008).

89. In particular, off-label use can be the norm where there are no alternative treatments, such as some types of cancer. Similarly, off-label use is common for children since most drugs are approved for use only on adults. Accordingly, the FDA has stated that off-label uses may be important or even constitute medically recognized standard of care in some situations. FDA Memorandum, *supra* note 6, at 17.

90. See Tewodros Eguale, David L. Buckeridge, Nancy E. Winslade, Andrea Benedetti, James A. Hanley & Robyn Tamblyn, *Drug, Patient, and Physician Characteristics Associated with Off-Label Prescribing in Primary Care*, 172 J. AM. MED. ASS'N: INTERNAL MED. 781, 783 (2012) (finding that seventy-nine percent of off-label prescriptions in Canada lacked strong scientific basis based on actual prescription data); David C. Radley, Stan N. Finkelstein & Randall S. Stafford, *Off-Label Prescribing Among Office-Based Physicians*, 166 J. AM. MED. ASS'N: INTERNAL MED 1021, 1025 (2006).

91. Randall S. Stafford, *Regulating Off-Label Drug Use—Rethinking the Role of the FDA*, 358 NEW ENG. J. MED. 1427, 1427 (2008).

92. HEALTH ACTION INT'L, *supra* note 41, at 29 (noting deaths from benfluorex, sold as Mediator when used off-label as appetite suppressant); Kate Cohen, *Fen Phen Nation*, PBS (Nov. 13, 2003), <https://www.pbs.org/wgbh/pages/frontline/shows/prescription/hazard/fenphen.html> [<https://perma.cc/S4N9-V6S4>] (noting that the FDA had to withdraw drugs commonly combined as “Fen Phen” from the market in 1997 after studies by the Mayo Clinic revealed the unapproved combination led to heart valve disease).

93. For example, Risperdal was marketed to doctors for elderly patients and used off label for dementia but can cause stroke-like attacks. Two years after such use, the manufacturer finally sent a warning to doctors regarding this problem after Canadian drug regulators issued a warning and only after FDA officials had enough information to compel the company to issue the warning. Alison Young & Chris Adams, *Prescribing Drugs “Off-Label” Is Routine, but Can Injure, Kill Patients*, MCCLATCHY DC BUREAU (Nov. 2, 2003, 6:32 PM), <https://www.mcclatchydc.com/news/politics-government/article24476629.html> [<https://perma.cc/74AP-KJG7>] (noting that a patient suffered stroke-like heart attacks while using Risperdal off-label).

94. In addition, sometimes off-label use puts patients at increased risk for serious diseases, such as cancer or Alzheimer's. This was the case with off-label prescribing of hormone replacements to address menopause symptoms such as hot flashes. Nelson et al., *supra* note 37, at 110–11 (explaining how hormone replacement is associated with risk of cancer).

95. For example, Rituxan was approved for non-Hodgkin's lymphoma, but when off-label prescriptions for a variety of unapproved uses led to severe and sometimes fatal reactions,

Notably, a recent study showed that adverse drug effects are more likely with off-label use, especially for those without strong scientific evidence, which constitutes the majority of such uses.<sup>96</sup> Finally, even if off-label use does not affirmatively harm patients, it may still be a poor use of drugs for essentially ineffective treatments and result in waste of resources. One prominent example involves Tamiflu, which was promoted off-label to reduce complications based on industry-financed articles; many governments stockpiled Tamiflu based on off-label promotion, as well as selective publication of only two of ten studies made available to the FDA.<sup>97</sup>

#### D. Introduction to Commercial Speech Law and Policy

The extent to which the FDA can regulate corporate speech surrounding off-label use of drugs fundamentally raises commercial speech issues under the First Amendment. Accordingly, this Section first explains what constitutes commercial speech. Then, this Section explains fundamental distinctions between how commercial and noncommercial speech are treated, as well as the reasons for the distinctions. Finally, this Section explains the test that has historically been used to assess whether government regulation of commercial speech is consistent with the First Amendment. This Section is intended to introduce the general issues, whereas later sections address how recent courts have addressed commercial speech that impacts off-label marketing more specifically.

An initial question is what constitutes commercial speech, since the government generally has more ability to regulate commercial speech.<sup>98</sup> There is more than one way that speech can be commercial, and thus subject to some governmental restrictions. Traditionally, speech has been considered commercial pursuant to a three-part test: (1) if it constitutes an advertisement, (2) refers to a specific product, or (3) is made with an economic motivation.<sup>99</sup> Speech that does all three of these is definitively commercial; drug company distribution of scientific articles regarding

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the FDA issued alerts and then a warning to the label. *Rituximab (Marketed As Rituxan) Information*, FOOD & DRUG ADMIN., <https://www.fda.gov/Drugs/DrugSafety/ucm109106.htm> [<https://perma.cc/PP5M-DYSM>]; see also Rosoff & Coleman, *supra* note 23, at 669–70 n.71.

96. Tewodros Eguale, David L. Buckeridge, Aman Verma, Nancy E. Winslade, Andrea Benedetti, James A. Hanley & Robyn Tamlyn, *Association of Off-Label Drug Use and Adverse Drug Events in an Adult Population*, 176 J. AM. MED. ASS'N: INTERNAL MED. 55 (2016); see also Aaron S. Kesselheim, John Connolly, James Rogers & Jerry Avorn, *Mandatory Disclaimers on Dietary Supplements Do Not Reliably Communicate the Intended Issues*, 34 HEALTH AFF. 438, 438 (2015) [hereinafter Kesselheim et al., *Mandatory Disclaimers*] (noting poor efficacy or harm in recent years with promotion of off-label uses).

97. E.g., HEALTH ACTION INT'L, *supra* note 41; Brownlee & Lenzer, *supra* note 38 (noting only two of ten studies published). This may have been an extreme case where the off-label use was suggested by the CDC, which has subsequently been revealed to have relied on industry funding. Lenzer, *supra* note 38.

98. Va. State Bd. of Pharmacy v. Va. Citizens Consumer Council, Inc., 425 U.S. 748, 781 (1976). However, before then, the Court had considered there to be no Constitutional restraint on “purely commercial advertising” that was well within the realm of “legislative judgment.” *Valentine v. Chrestensen*, 316 U.S. 52, 54 (1942).

99. *Va. State Bd. of Pharmacy*, 426 U.S. at 761, 781.

off-label uses of their drugs to doctors has been found to meet all three.<sup>100</sup> In addition, what is considered commercial speech has expanded in recent years.<sup>101</sup>

First Amendment jurisprudence has traditionally treated commercial speech differently than noncommercial speech. Noncommercial speech that is traditionally considered at the core of the First Amendment, such as political or religious speech, is generally immune from government restriction since restrictions are invalid unless they pass strict scrutiny.<sup>102</sup> Commercial speech, on the other hand, has traditionally been evaluated under a more lenient intermediate scrutiny test, as explained below.<sup>103</sup> The differing levels of scrutiny have generally resulted in individuals having a right to freely express opinions, including false ones, whereas governments have traditionally been permitted to regulate clearly false and misleading commercial statements.

The reason for the difference relates to the underlying policy distinctions. In particular, all speech of individuals is considered to promote a “marketplace of ideas” that fosters better-informed citizenry, and is consistent with democratic self-determination;<sup>104</sup> the democratic tie-in is important to permitting any individual to freely express opinions, including ones that are false.<sup>105</sup> This rationale also explains the few situations where individual speech is not protected, including fighting words and obscenity, which do not involve reasoned and deliberative response.<sup>106</sup> Although a “marketplace of ideas” has been referenced in the context of commercial speech, it is generally only in the context of making intelligent decisions based on the free flow of commercial information without any tie to democratic principles.<sup>107</sup>

Notably, commercial speech has historically only been protectable under the First Amendment because the information is valuable to the *audience*, but not because the speaker has any right to speak.<sup>108</sup> This policy distinction is why the government can

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100. Wash. Legal Found. v. Friedman, 13 F. Supp. 2d 51, 64 (D.D.C. 1998).

101. See Sorrell v. IMS Health Inc., 564 U.S. 552, 568–71 (2011); Citizens United v. FEC, 558 U.S. 310 (2010).

102. Of course, this does not apply to speech that has no informational value, such as obscenity or fighting words. See *infra* note 106.

103. Sorrell obviously suggests that commercial speech regulation is subject to heightened scrutiny based on viewpoint targeting, although what this means is still unclear. 564 U.S. 552.

104. See *id.* at 583.

105. See United States v. Alvarez, 567 U.S. 709, 718 (2012); Jennifer M. Keighley, *Can You Handle the Truth? Compelled Commercial Speech and the First Amendment*, 15 U. PA. J. CONST. L. 539, 551 (2012).

106. Miller v. California, 413 U.S. 15, 24 (1973) (denying First Amendment protection to sexual materials with no “literary, artistic, political, or scientific value”); Brandenburg v. Ohio, 395 U.S. 444 (1969) (barring speech that is likely to incite imminent lawless action); Chaplinsky v. New Hampshire, 315 U.S. 568, 571–72 (1942) (noting that profane, libelous, and “fighting” words “are no essential part of any exposition of ideas, and are of such slight social value as a step to truth that any benefit that may be derived from them is clearly outweighed by the social interest in order and morality”).

107. See, e.g., Va. State Bd. of Pharmacy v. Va. Citizens Council, Inc., 425 U.S. 748, 760 (1976).

108. E.g., Ohralik v. Ohio State Bar Ass’n, 436 U.S. 447, 456 (1978) (noting that the state right to regulate some commercial speech is because commercial speech is not a speaker-oriented autonomy right and thus gets more limited protection); Keighley, *supra* note 105, at

sometimes regulate commercial speech and, even in some cases, *mandate* that commercial speakers provide information to consumers under some situations based on the same principle that commercial speech should inform consumers.<sup>109</sup> Although one scholar has argued First Amendment law, including commercial speech, recognizes speaker rights,<sup>110</sup> courts have thus far not explicitly noted any reason to depart from the traditional audience-centric rationale for commercial speech.<sup>111</sup>

The traditional framework for analyzing whether regulation of commercial speech is permissible is according to the intermediate scrutiny test first announced by the Supreme Court's 1980 decision in *Central Hudson*.<sup>112</sup> More recently, the Supreme Court majority in *Sorrell v. IMS Health Inc.* applied the *Central Hudson* test<sup>113</sup> even though it controversially suggested that a regulation targeting commercial speech of pharmaceutical companies should be subject to stricter scrutiny.<sup>114</sup> The *Sorrell*

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554; Robert Post & Amanda Shanor, *Adam Smith's First Amendment*, 128 HARV. L. REV. 165, 170, 172 (2015); Shanor, *supra* note 8, at 146 (noting that commercial speech doctrine was created as a tool of consumer protection during the consumer protection movement, and not to promote autonomy interests of commercial speakers). In addition, many believe that the doctrine of free speech generally is intended to focus on right of audiences to access ideas without governmental interference, rather than the rights of speakers. *E.g.*, Daniel A. Farber, *Free Speech Without Romance: Public Choice and the First Amendment*, 105 HARV. L. REV. 554, 558–59 (1991); Eugene Volokh, *The Freedom of Speech and Bad Purposes*, 63 UCLA L. REV. 1366, 1370–71 (2016).

109. *Zauderer v. Office of Disciplinary Counsel*, 471 U.S. 626 (1985). However, the government can only compel speech that is purely factual and noncontroversial, which has recently been at issue with FDA regulations that aimed to require mandatory images on tobacco labeling. As one court noted, although the images are not “patently false,” they can also be misunderstood or intended to evoke an emotional response. *R.J. Reynolds Tobacco Co. v. FDA*, 696 F.3d 1205, 1216–17 (D.C. Cir. 2012); *see also* *Dist. Tobacco City & Lottery, Inc. v. United States*, 674 F.3d 509, 560–61 (6th Cir. 2012) (finding that pictures are inherently persuasive).

110. Leslie Kendrick, *Are Speech Rights for Speakers*, 103 VA. L. REV. 1767 (2017).

111. One commentator suggests *Sorrell's* majority was wrong to ignore the value, or, rather, *lack* of value of detailing information for doctors. Alan B. Morrison, *No Regrets (Almost): After Virginia Board of Pharmacy*, 25 WM. & MARY BILL OF RTS. J. 949, 959 (2017).

112. *Cent. Hudson Gas & Elec. Corp. v. Pub. Serv. Comm'n*, 447 U.S. 557 (1980).

113. 564 U.S. 552 (2011). Since the government regulation did not pass the intermediate test, arguably there was no need to consider whether it would pass a heightened test. *Id.* at 583–84.

114. *Id.* at 564–67. However, this is contrary to traditional commercial speech law that generally permits direct regulation of content, even though this is not permissible regarding speech of individuals. *Cent. Hudson*, 447 U.S. at 564 n.6. As some have noted, commercial speech regulation is, by its very nature, content-based, such that this suggested standard would threaten widely accepted regulatory activity. *See Sorrell*, 564 U.S. at 589 (Breyer, J., dissenting) (noting that “regulatory programs necessarily draw distinctions on the basis of content” and that it is not unusual for some regulations to be “speaker-based” affecting only a class of entities, i.e. the regulated ones); Tamara R. Piety, “*A Necessary Cost of Freedom?*” *The Incoherence of Sorrell v. IMS*, 64 ALA. L. REV. 1, 5 (2012) (“*Sorrell's* reasoning eviscerates the rationale on which *Virginia Pharmacy* was based—protection of listeners’ interests—and substitutes for it a rationale which elevates the interests of commercial speakers over that of listeners, such that even where the speech presents a *detriment* to listeners, it is

majority opinion did not articulate a specific test and subsequent courts have similarly applied the same *Central Hudson* test.<sup>115</sup> Accordingly, that remains the current framework for analysis. There are four parts to analyze under *Central Hudson* in terms of whether expression can be properly regulated by the federal or state government. For commercial speech to be potentially protected, it must first concern lawful activity and not be actually misleading. Second, the government interest in regulating the speech must be substantial. Assuming both of those are satisfied, the third and fourth questions are whether the government regulation directly advances that interest, and whether it is more extensive than necessary to serve that interest.

The first aspect of the *Central Hudson* inquiry permits the government to entirely ban commercial speech that is false or misleading. There is no First Amendment protection for such speech because there is no information value in inaccurate speech that is more likely to deceive than inform.<sup>116</sup> Although the Supreme Court has framed this inquiry around whether information is false or misleading, the only type of information that is absolutely barred is *inherently*, rather than only potentially, false or misleading information. The government has the burden to establish inherently misleading information, which is a high standard. This tough standard has been rationalized as applicable because the government would otherwise get a “free pass” without considering other *Central Hudson* factors.<sup>117</sup> On more than one occasion, courts have been reluctant to accept FDA assertions that the relevant audience will be misled without empirical support of such confusion.<sup>118</sup>

If information is truthful, but *potentially* misleading, government regulation depends upon the three other factors. In particular, the government must have a “substantial interest” in the regulation, the regulation must “directly” advance the

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protected because of its value to the *speaker*.” (emphasis in original)); Shanor, *supra* note 8, at 146 (noting that commercial speech is content based).

115. See, e.g., *Amarin Pharma, Inc. v. FDA*, 119 F. Supp. 3d 196 (S.D.N.Y. 2015). *Caronia*’s majority stated that strict scrutiny applied, but actually applied the *Central Hudson* test. *United States v. Caronia*, 703 F.3d 149, 164–65 (2d Cir. 2012).

116. *Cent. Hudson*, 447 U.S. at 563–64.

117. E.g., Rodney A. Smolla, SMOLLA & NIMMER, COMMERCIAL SPEECH 20:15 (2017 Update) (considering it “drastic medicine” to treat a statement as inherently misleading because that would give regulators a “free pass” from the usual requirement of proof and causation” and suggesting suggesting courts treat claims with a “healthy dose of skepticism”).

118. This was true in a number of cases involving marketing of dietary supplements to consumers. E.g., *Int’l Dairy Foods Ass’n v. Boggs*, 622 F.3d 628, 637 (6th Cir. 2010) (concluding that proposed claim informs consumers of a “meaningful distinction,” contrary to FDA position and “at worst . . . misleads” them to believe that milk untreated with rbST harms their health); *Pearson v. Shalala*, 164 F.3d 650, 655 (D.C. Cir. 1999) (dismissing FDA concerns of consumer confusion and analogizing FDA presumptions concerning consumers as based on mistaken presumption that “consumers were asked to buy something while hypnotized, and therefore they are bound to be misled”). In fact, one court even asserted that it would not be inclined to find statements to be inherently misleading without proof of two different things: minimal factual support for the allegedly false statement *and* empirical support that consumers would be confused. *Whitaker v. Thompson*, 248 F. Supp. 2d 1, 10 (D.D.C. 2002) (citing *Pearson*, 164 F.3d at 659–60). Although there is an argument that consumers may be more likely confused by marketing than doctors, the same burden of proof would apply to an argument that doctors are confused.

government interest, and the regulation must be no more extensive than necessary.<sup>119</sup> In other words, even if the government has a substantial interest in the regulation, a complete ban might not withstand First Amendment scrutiny if it is considered more restrictive than necessary to serve that interest.

In many situations involving government interest regarding regulation of commercial speech relating to foods and drugs, courts have overruled government regulations, finding them more extensive than necessary. For example, *Thompson v. Western States*, the first Supreme Court commercial speech case involving drugs, held in a 5-4 decision that specialty compounding pharmacies were permitted to advertise their products (and could not be banned from all advertising) because there were other nonspeech restrictions that could be used to satisfy the government interest in discouraging large-scale manufacturing by these pharmacies, such as forbidding or limiting compounded drug sales.<sup>120</sup> Also, in *Washington Legal Foundation v. Friedman*, the District Court for the District of Columbia similarly found prior FDA regulations regarding distribution of scientific articles and industry-sponsored education relating to off-label use to be overly restrictive on speech.<sup>121</sup> This was based on an assumption that providing complete disclosure of the manufacturer interest would be a less burdensome restriction.<sup>122</sup> Along similar lines, courts have invalidated FDA regulations that attempt to bar health claims for dietary supplements without significant scientific support; although the courts recognized a substantial interest in protecting consumers from deceptive marketing practices, the courts found a complete bar more extensive than necessary without empirical proof that a disclaimer would fail to correct deceptiveness.<sup>123</sup>

## II. REVEALING AND DEBUNKING SCHEMAS THAT SUPPORT FIRST AMENDMENT FALLACIES

This Part explains the existence of two distinct schemas that courts have perpetuated in cases expanding commercial speech protection for pharmaceutical marketing: the sophisticated doctor schema and the more information schema. These schemas are not intended to entirely account for all of commercial speech jurisprudence. Instead, the goal is to show that some legal presumptions reflect these schemas rather than empirically supported fact. Understanding these schemas helps shed light on recent First Amendment cases discussed in Part III, and also serves as

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119. *Cent. Hudson*, 447 U.S. at 566.

120. *Thompson v. W. States Med. Ctr.*, 535 U.S. 357 (2002). The relatively lax oversight of drug compounding has failed to promote public health. For example, in 2012, over 60 people were killed and over 700 suffered from meningitis when a company shipped contaminated drugs. Doris Browne, *Fixing a Crisis of Confidence in Drug Compounding*, WASH. EXAMINER (Jan. 16, 2018, 7:00 AM), <https://www.washingtonexaminer.com/fixing-a-crisis-of-confidence-in-drug-compounding/article/2645969> [<https://perma.cc/2QGL-BECU>].

121. 13 F. Supp. 2d 51, 72–73 (D.D.C. 1998).

122. *Id.*

123. *Pearson*, 164 F.3d. 650; *Whitaker*, 248 F. Supp. 2d 1. However, in the case of dietary supplements, it has been noted that the potential for deception is “severely limited,” in that no serious physical harm will result from consumption of such supplements. *Whitaker*, 248 F. Supp. 2d at 16.

an important foundation for proposed changes suggested in Part IV. This Part begins with an introduction to schemas based on the literature on cognitive biases. Then, the existence of each schema in the case law is discussed before explaining why the schema is not completely supported by fact.

#### A. Introduction to Schemas

This Section provides fundamental information concerning key aspects from the vast areas of cognitive bias and behavioral economics that is essential to understanding the existence of two key schemas introduced in the next two sections. Essentially, researchers in these areas have repeatedly shown that all individuals, regardless of education or experience, acquire and process information subject to certain largely subconscious mental flaws. In particular, although individuals believe that they approach information systematically and with deductive reasoning, research shows this is often not the case due to reliance on cognitive biases, heuristics, and schemas, which are essentially mental shortcuts.<sup>124</sup> Incomplete cognitive processing is actually considered adaptive to deal with an information-rich world and especially to help efficiently deal with ambiguous situations and/or time-limited situations.<sup>125</sup> On some level, individuals seem to intuit this since people often believe that others are subject to bias—while simultaneously discounting the possibility of having their own bias.<sup>126</sup> Although all individuals are subject to cognitive biases, doctors may be especially likely to use such processing not only because they are busy, but also because the process of diagnosis often involves ambiguity and incomplete

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124. See DANIEL KAHNEMAN, *THINKING FAST AND SLOW* (2011).

125. In addition, although literature often refers to cognitive biases and the word “bias” may suggest a flaw, they are important for psychological well-being. See Jeffrey J. Rachlinski, *The Uncertain Psychological Case for Paternalism*, 97 NW. U. L. REV. 1165, 1172 (2003) (only individuals free of biased self-perceptions suffered from clinical depression); see also LEON FESTINGER, *A THEORY OF COGNITIVE DISSONANCE* 2–3 (1957) (noting that individuals are motivated to ignore or discredit information inconsistent with prior views to prevent psychological distress that would otherwise result; in other words, people try to avoid “cognitive dissonance”).

126. This is referred to as naïve realism. Robert J. Robinson, Dacher Keltner, Andrew Ward & Lee Ross, *Actual Versus Assumed Differences in Construal: “Naive Realism” in Intergroup Perception and Conflict*, 68 J. PERSONALITY & SOC. PSYCHOL. 404, 404 (1995); Brad J. Sagarin, Robert B. Cialdini, William E. Rice & Sherman B. Serna, *Dispelling the Illusion of Invulnerability*, 83 J. PERSONALITY & SOC. PSYCHOL. 526 (2002). For example, in the 2012 presidential election, some Republicans assumed Nate Silver was biased, and thus, his data predicting an Obama win was suspect. Nate Silver, *When Internal Polls Mislead, a Whole Campaign May Be to Blame*, N.Y. TIMES: FIVETHIRTYEIGHT (Dec. 1, 2012, 6:01 AM), <http://fivethirtyeight.blogs.nytimes.com/2012/12/01/when-internal-polls-mislead-a-whole-campaign-may-be-to-blame> [https://perma.cc/33NV-S4P7].

information,<sup>127</sup> which studies repeatedly show are situations where individuals are especially likely to rely on cognitive biases.<sup>128</sup>

### 1. Schemas Shape Information Processing

An important type of cognitive flaw in processing information for this Article is a *schema*. Essentially, a schema is a mental framework through which individuals perceive and filter information.<sup>129</sup> Schemas are developed through concrete experiences as well as personal morals and societal roles; some examples of schemas that are part of popular culture include lawyers as mercenaries, women as shoppers, and men as relationship avoidant. Schemas operate like other cognitive flaws by occurring largely outside of conscious awareness.

All individuals, including highly educated individuals such as doctors, scientists, and judges, hold schemas. Doctors are vulnerable to relying on schemas since the process of diagnosis typically involves great ambiguity, a situation in which schemas flourish.<sup>130</sup> Studies indicate that doctors tend to generate an early hypothesis that impacts subsequent information gathering and may result in a faulty diagnosis.<sup>131</sup> Similarly, doctors may have schemas that impact how they prescribe drugs; they could assume that new drugs are superior, or, alternatively, that new drugs pose more risks.<sup>132</sup>

Importantly, a schema impacts how new information is perceived. So, for example, news that a huge iceberg has broken off from the Antarctic shelf is likely perceived differently by those who believe in global warming, versus those who do not.<sup>133</sup> Schemas also impact how individuals perceive accuracy of information, as

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127. See Mark A. Hall, *Institutional Control of Physician Behavior: Legal Barriers to Health Care Cost Containment*, 137 U. PA. L. REV. 431, 480–82 (1988) (noting that, contrary to the assumption that doctors systematically evaluate possible treatments, they rely on general rules or “heuristics” to deal with the fact that uncertainty pervades practices, given that many procedures have not been subject to rigorous clinical trials); Jessica Mantel, *The Myth of the Independent Physician: Implications for Health Law, Policy and Ethics*, 64 CASE W. RES. L. REV. 455, 471 (2013); see also CONGRESSIONAL BUDGET OFFICE, RESEARCH ON THE COMPARATIVE EFFECTIVENESS OF MEDICAL TREATMENTS 9 (2007) (noting that less than half of medical decisions are supported by adequate evidence regarding effectiveness).

128. E.g., Dennis A. Gioia & Peter P. Poole, *Scripts in Organizational Behavior*, 9 ACAD. MGMT. REV. 449, 454 (1984).

129. AUGOSTINOS ET AL., *supra* note 3, at 68–69.

130. Mark P. Higgins & Mary P. Tully, *Hospital Doctors and Their Schemas About Appropriate Prescribing*, 39 MED. EDUC. 184 (2005).

131. Elke U. Weber, Ulf Böckenholt, Denis J. Hilton & Brian Wallace, *Determinants of Diagnostic Hypothesis Generation: Effects of Information, Base Rates, and Experience*, 19 J. EXPERIMENTAL PSYCHOL. 1151 (1993).

132. See Cynthia M. Ho, *Drugged Out: How Cognitive Bias Hurts Drug Innovation*, 51 SAN DIEGO L. REV. 419, 499–504 (2014); Peter R. Mansfield, *Healthy Skepticism’s New AdWatch: Understanding Drug Promotion*, 179 MED. J. AUST. 644 (2003) [hereinafter Mansfield, *Healthy Skepticism*]; Clement J. McDonald, *Medical Heuristics: The Silent Adjudicators of Clinical Practice*, 124 ANNALS INTERNAL MED. 56, 57, 59 (1996).

133. Compare Ilissa Ocko, *Huge Antarctic Iceberg Breaks Off. Here’s Why It Worries Scientists*, ENVTL. DEF. FUND (July 12, 2017), <https://www.edf.org/blog/2017/07/12/huge>



well as whether that information is persuasive. The same information will be processed differently by those with different schemas. More specifically, schemas can influence the extent to which an individual considers or discounts research results depending on whether or not it is consistent with their schema.<sup>134</sup>

## 2. Schemas are Reinforced by Other Cognitive Biases

Schemas are notably resistant to change. According to research, the more people rely on a schema, the more the schema is resistant to any inconsistent evidence, since schemas dictate what information an individual will remember.<sup>135</sup> In other words, once a schema is established, individuals view new information consistent with that schema and even seek out similar information. Schemas are often maintained by a host of ancillary cognitive biases including confirmation bias, availability, and overconfidence;<sup>136</sup> studies have found doctors to rely on these and other cognitive biases.<sup>137</sup>

Confirmation bias is very important to maintaining a schema. This refers to the tendency to view information consistent with preconceptions and even skew searches for more information to be consistent with such preconceptions.<sup>138</sup> Essentially,

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-antarctic-iceberg-breaks-heres-why-it-worries-scientists [<https://perma.cc/D6WH-NM32>], with Dave Mosher, *Scientists Say the Delaware-Size Iceberg that Broke Off Antarctica Could Have Happened Without Global Warming*, BUS. INSIDER (July 18, 2017, 3:29 PM), <https://www.businessinsider.com/iceberg-a68-did-climate-change-cause-crack-2017-7> [<https://perma.cc/2G9A-B64K>]; see also Justin Worland, *New Discovery in Antarctica Suggests Ice Sheets Could Disappear Way Faster than Previously Thought*, TIME (Apr. 19, 2017), <http://time.com/4745827/antarctica-water-climate-change> [<https://perma.cc/U8UJ-W5VP>].

134. In a classic study, subjects were preselected based on their preference for or against capital punishment. Individuals were more critical of research methods inconsistent with their beliefs, citing issues such as insufficient sample size, nonrandom sample selection, or absence of control for key variables. Charles G. Lord, Lee Ross & Mark R. Lepper, *Biased Assimilation and Attitude Polarization: The Effects of Prior Theories on Subsequently Considered Evidence*, 37 J. PERSONALITY & SOC. PSYCHOL. 2098 (1979); see also Harold H. Kassarjian & Joel Benjamin Cohen, *Cognitive Dissonance and Consumer Behavior*, 8 CAL. MGMT. REV. 55 (1965) (smokers were motivated to disregard evidence of health risks of smoking); Ziva Kunda, *The Case for Motivated Reasoning*, 108 PSYCHOL. BULL. 480, 490 (1990) (showing subjects with high caffeine consumption likely to disbelieve article that supposedly correlated caffeine with a serious disease and to consider the research less sound).

135. E.g., RICHARD E. NISBETT & LEE ROSS, HUMAN INFERENCE: STRATEGIES AND SHORTCOMINGS OF SOCIAL JUDGMENT 146–50 (1980).

136. In addition, a schema may be also reinforced by “anchoring,” a cognitive bias that gives undue weight to initial information. Amos Tversky & Daniel Kahneman, *Judgment Under Uncertainty: Heuristics and Biases*, 185 SCI. 1124, 1128 (1974). So, once a schema is established, it may have an anchoring effect against which new information is processed.

137. E.g., Gustavo Saposnik, Donald Redelmeier, Christian C. Ruff & Philippe N. Tobler, *Cognitive Biases Associated with Medical Decisions: A Systematic Review*, 16 BIOMED CENT. 138 (2016) (finding that all studies over a thirty-five year period indicate doctors are subject to at least one cognitive bias and certain ones are associated with diagnostic errors, including overconfidence).

138. Internet searches can even feed into this since current algorithms are designed to tailor search results to prior searches.

people see what they want to see. So, individuals with different prior beliefs may have very different reactions to the same “facts” (i.e., they will be more likely to accept new information similar to existing views and be skeptical to information that is inconsistent with those views). Confirmation bias is most likely to play a role when trying to comprehend ambiguous information that would be more susceptible to different interpretations.<sup>139</sup> In such situations, individuals with opposing schemas may become more rooted in those schemas after viewing the same “evidence.”<sup>140</sup> In addition, even if the conclusion from our confirmation biases is objectively unsupported, the bias is difficult to combat.<sup>141</sup> Studies have shown that even after information is discredited an individual may continue to believe it; empirical studies have shown this is the case with the myth that President Obama is not a U.S. citizen, and especially so among conservatives who would typically be more likely to hold a negative view of him.<sup>142</sup>

Doctors are also subject to confirmation bias. Doctors may favor their initial hypotheses or assumptions due to confirmation bias.<sup>143</sup> For example, while some doctors erroneously assumed most patients are resistant to aspirin as a low-cost diuretic, which some companies with more expensive drug alternatives to aspirin had promoted, this assumption was recently shown to have no scientific justification.<sup>144</sup> Doctors could have been influenced by company advertising to favor the self-interested corporate idea that patients are resistant to aspirin as a type of confirmation bias.

The creation, as well as propagation, of a schema can also be related to the “availability” bias. Essentially, this cognitive shortcut refers to individuals more easily recalling readily accessible information and assuming it is necessarily important. In the medical context, the availability heuristic may explain why a 2005

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139. One of the most striking examples is that researchers found that conservatives assumed that the political satire *The Colbert Report*, was in fact truthful because the show reflected their own political view. Heather L. LaMarre, Kristen D. Landreville & Michael A. Beam, *The Irony of Satire: Political Ideology and the Motivation to See What You Want to See in The Colbert Report*, 14 INT’L J. PRESS/POL. 212, 222–23 (2009).

140. For example, believers and nonbelievers became more entrenched in their views after reading a fictitious report concerning religious resurrection. C. Daniel Batson, *Rational Processing or Rationalization?: The Effect of Disconfirming Information on a Stated Religious Belief*, 32 J. PERSONALITY & SOC. PSYCHOL. 176, 176 (1975); see also Lord et al., *supra* note 134 (finding similar results after subjects were provided “evidence” about the deterrent effects of capital punishment).

141. E.g., George Loewenstein, Samuel Issacharoff, Colin Camerer & Linda Babcock, *Self-Serving Assessments of Fairness and Pretrial Bargaining*, 22 J. LEGAL STUD. 135, 139 (1993).

142. E.g., Brendan Nyhan & Jason Reifler, *When Corrections Fail: The Persistence of Political Misperceptions*, 32 POL. BEHAV. 303, 323 (2010).

143. See Weber et al., *supra* note 131.

144. Tilo Grosser, Susanne Fries, John A. Lawson, Shiv C. Kapoor, Gregory R. Grant & Garret A. FitzGerald, *Drug Resistance and Pseudoresistance: An Unintended Consequence of Enteric Coating Aspirin*, 127 CIRCULATION 377, 382–83 (2013); Katie Thomas, *Study Raises Questions on Coating of Aspirin*, N.Y. TIMES (Dec. 4, 2012), <https://www.nytimes.com/2012/12/05/business/coating-on-buffered-aspirin-may-hide-its-heart-protective-effects.html> [<https://perma.cc/V2WH-CRNV>].

study found that doctors were undertreating patients' pain because they had concerns about addiction to painkillers due to the high publicity of opiate addiction.<sup>145</sup> The availability heuristic can impact the strength of a schema. If information is more available in the sense of being repeated, it is presumed correct.<sup>146</sup> Moreover, the repetition of information is often remembered even better than its source,<sup>147</sup> with repeated information often assumed to be from a credible source when the source is not recalled.<sup>148</sup> Repeated information is especially powerful to individuals that lack motivation or opportunity to scrutinize the message.<sup>149</sup> Notably, even when individuals are told that repeated statements are not more likely to be true or even that the source of the information is biased, they still seem inclined to assume repeated statements are true.<sup>150</sup> This is especially relevant to the context of pharmaceutical marketing to doctors who realize that information from companies is likely to be biased. In particular, this data suggests that doctors repeatedly told information from companies may assume that company information is true.

In addition, a schema may be supported by an overconfidence bias.<sup>151</sup> The overconfidence bias refers to an individual's overestimation of likely being correct regarding abilities or knowledge.<sup>152</sup> For example, the vast majority of entering law students believe they will be in the top ten percent of the class when, statistically, that is impossible. The overconfidence bias applies to all individuals, including

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145. See Jill G Klein, *Five Pitfalls in Decisions About Diagnosis and Prescribing*, 330 BRIT. MED. J. 781, 782 (2005).

146. See KAHNEMAN, *supra* note 124, at 129–35.

147. Danielle C. Polage, *Making Up History: False Memories of Fake News Stories*, 8 EUR. J. PSYCHOL. 245, 248–49 (2012).

148. Alison R. Fragale & Chip Heath, *Evolving Informational Credentials: The (Mis)attribution of Believable Facts to Credible Sources*, 30 PERSONALITY & SOC. PSYCHOL. BULL. 225, 225–26 (2004); Kimberlee Weaver, Stephen M. Garcia, Norbert Schwarz & Dale T. Miller, *Inferring the Popularity of an Opinion from Its Familiarity: A Repetitive Voice Can Sound Like a Chorus*, 92 J. PERSONALITY & SOC. PSYCHOL. 821, 821–22 (2007).

149. Scott A. Hawkins & Stephen J. Hoch, *Low Involvement Learning: Memory Without Evaluation*, 19 J. CONSUMER RES. 212, 212–13 (1992); see also Sunita Sah, Don A. Moore & Robert J. MacCoun, *Cheap Talk and Credibility: The Consequences of Confidence and Accuracy on Advisor Credibility and Persuasiveness*, 121 ORGANIZATIONAL BEHAV. & HUM. DECISION PROCESSES 246 (2013) (individuals are strongly influenced by confident messages and will not attempt to ascertain whether the message is correct if that requires effort).

150. Linda A. Henkel & Mark E. Mattson, *Reading Is Believing: The Truth Effect and Source Credibility*, 20 CONSCIOUSNESS & COGNITION 1705, 1705–06 (2011); see also Frederick T. Bacon, *Credibility of Repeated Statements*, 5 J. EXPERIMENTAL PSYCHOL.: HUM. LEARNING & MEMORY 241, 251 (1979) (showing that repeated statements are more likely to be judged as true, whereas contrary statements are likely to be viewed as false).

151. Doctors likely also overestimate the effectiveness of patient treatments pursuant to an over optimism bias, pursuant to which an individual may overestimate likely positive outcomes. Tali Sharot, *The Optimism Bias*, 21 CURRENT BIOLOGY R941, R943 (2011). This may not perpetuate a schema, but could make doctors vulnerable to marketing.

152. Barbara Mellers & A. Peter McGraw, *Self-Serving Beliefs and the Pleasure of Outcomes*, in 2 THE PSYCHOLOGY OF ECONOMIC DECISIONS: REASONS AND CHOICES 31, 37 (Isabelle Brocas & Juan D. Carrillo eds., 2004); Rachlinski, *supra* note 125, at 1172–73.

doctors.<sup>153</sup> A doctor or judge may thus be overly confident that his schema is correct and maintain it even in the face of contradictory evidence.

Although there are many individual cognitive biases, these examples should underscore how schemas become entrenched and difficult to combat, even in the face of contrary evidence. There is no comprehensive list of schemas, since they are informed, in part, by individual experience. However, as discussed in the next sections, there are two key schemas that have played an important role in commercial speech jurisprudence regarding off-label marketing.

### *B. The Sophisticated Doctor Schema*

This Section argues that there is an important, yet generally unrecognized, schema overemphasizing how sophisticated doctors are in evaluating information from companies, including marketing information, as well as peer review publications. Although considering doctors more knowledgeable than lay consumers is consistent with other areas of the law, such as the learned intermediary doctrine,<sup>154</sup> the sophisticated doctor schema may result in courts unrealistically assuming that doctors are invulnerable to marketing influences. This Section first provides evidence of the schema in court opinions, as well as from scholarly literature and doctors themselves. Then, this Section will explain why this schema is fundamentally not empirically supported, even if it is a widespread presumption.

#### 1. What Is the Sophisticated Doctor Schema?

In *Washington Legal Foundation v. Friedman*,<sup>155</sup> the sophisticated doctor schema played an important role in the first direct challenge to FDA regulation of off-label promotion. In this case, Washington Legal Foundation, an organization that focuses on challenging “undue influence from government” regulation,<sup>156</sup> challenged two FDA guidance documents, one of which intended to restrict the type of printed materials manufacturers could provide doctors concerning off-label uses and the other intending to limit manufacturer involvement in continuing medical

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153. See Andrea O. Baumann, Raisa B. Deber & Gail G. Thompson, *Overconfidence Among Physicians and Nurses: The ‘Micro-Certainty, Macro-Uncertainty’ Phenomenon*, 32 SOC. SCI. MED. 167, 172–73 (1991) (doctors overconfident in “correct” treatment in situation where there was no empirically supported superior method of treatment); François Laure, Sophie M. Colleau, Alain Fontaine & Louis Brasseur, *Oncologists and Primary Care Physicians’ Attitudes Toward Pain Control and Morphine Prescribing in France*, 76 CANCER 2375 (1995) (explaining that doctors are overly confident in the ability to control pain).

154. See *Sterling Drug Inc. v. Cornish*, 370 F.2d 82, 85 (8th Cir. 1966). However, whether this doctrine is applicable has been challenged by one scholar. Kate Greenwood, *Physician Conflicts of Interest in Court: Beyond the “Independent Physician” Litigation Heuristic*, 30 GA. ST. U. L. REV. 759 (2014).

155. 13 F. Supp. 2d 51, 54 (D.D.C. 1988).

156. *Wash. Legal Found.*, 13 F. Supp. 2d at 54 (quoting from complaint); see also *About WLF*, WASH. LEGAL FOUND., <https://www.wlf.org/about-washington-legal-foundation/> [<https://perma.cc/C9CN-ENXC>].

education.<sup>157</sup> The district court held that the FDA guidance documents were unconstitutional violations of commercial speech rights<sup>158</sup> despite the government interest in encouraging supplemental applications for new drug uses because the regulation was viewed as more extensive than necessary.<sup>159</sup> The court recognized that since companies clearly want to increase sales,<sup>160</sup> they would likely aggressively promote a single article supporting use of a drug—even if there is considerable evidence to the contrary—with a potential to mislead.<sup>161</sup> Nonetheless, when it applied the *Central Hudson* test, the court seemed unconcerned about the potential to mislead physicians. It stated that “despite the FDA’s occasional statements in its briefs to the contrary, physicians are a highly educated, professionally-trained and *sophisticated* audience”<sup>162</sup> in contrast with the “general consumer public.”<sup>163</sup>

The *Washington Legal Foundation* court seemed strongly influenced by the sophisticated doctor schema in rejecting out of hand the FDA’s interest in ensuring doctors have accurate and unbiased information. The court asserted that the FDA’s interest in providing doctors complete and unbiased information was *not* a substantial government interest that could support government regulation pursuant to the *Central Hudson* test.<sup>164</sup> The court asserted that doctors are “certainly capable of critically evaluating” information provided by self-interested companies.<sup>165</sup> The court claimed that it was “unclear” why a doctor might not critically evaluate scientific findings if presented by a company, even though earlier in the opinion the court noted that companies have an interest in selectively providing partial information to doctors.<sup>166</sup>

An important part of the sophisticated doctor schema is the idea that doctors are capable of evaluating articles provided by self-interested companies concerning whether an unapproved use of a drug is effective, such that there is no need to rely on the FDA to assess whether drugs are safe and effective. For example, the *Washington Legal Foundation* court stated that “a physician’s livelihood depends upon the ability to make accurate, life-and-death decisions based upon the scientific evidence before them. They are certainly capable of critically evaluating journal

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157. Final Guidance on Industry-Supported Scientific and Educational Activities, 62 Fed. Reg. 64074 (Dec. 3, 1997); Advertising and Promotion; Guidance, 61 Fed. Reg. 52800 (1996).

158. *Wash. Legal Found.*, 13 F. Supp. 2d at 74 (finding guidance documents more extensive than necessary, such that the fourth prong of the *Central Hudson* test fails); *see also* *Thompson v. W. States Med. Ctr.*, 535 U.S. 357, 374 (2002) (noting that it is a “questionable assumption that doctors would prescribe unnecessary medications,” with regard to the possibility that doctors might prescribe drugs that are advertised to consumers, in striking down a ban against advertising of compounded drugs).

159. *Wash. Legal Found.*, 13 F. Supp. 2d at 69.

160. *Id.* at 64.

161. *Id.* at 65.

162. *Id.* at 63 (emphasis added).

163. *Id.* at 70 (“[M]anufacturers are not seeking to distribute this information to the general consumer public, who likely lack the knowledge or sophistication necessary to make informed choices on the efficacy of prescription drugs.”).

164. *Id.* at 69–70.

165. *Id.* at 70; *see also id.* at 69 (asserting that limiting material from doctors out of concern for doctor misuse to be “wholly and completely unsupportable”).

166. *Id.* at 70.

articles or textbook reprints that are mailed to them, or the findings presented at CME seminars.”<sup>167</sup> The fact that doctors may be making life-and-death decisions based on such information does not mean that the incomplete information is not misleading. In addition, even if doctors realize the information is biased, and somewhat discount the results as more favorable than necessary, doctors still lack complete information.

Since *Washington Legal Foundation*, the sophisticated doctor schema has been embraced not only by other courts, as will be subsequently discussed in Part III, but also by physicians. For example, some doctors participated as plaintiffs alongside the company Amarin that was seeking to promote off-label uses of its drugs in a suit challenging FDA regulations limiting off-label promotion on First Amendment grounds.<sup>168</sup> These doctors clearly do not share the FDA’s concern that they may be misled by drug manufacturers; rather, they assume that information from companies will be valuable.<sup>169</sup>

The views of the doctors in this suit are consistent with other studies indicating that doctors have a generally positive view regarding the most common type of information from companies: pharmaceutical detailing (i.e., information from individual sales representative visits to doctors). Although some doctors recognize detailing information may be biased or inaccurate,<sup>170</sup> many consider detailing to be a valuable source of information.<sup>171</sup> Most studies indicate that doctors believe their

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167. *Id.*

168. *Amarin Pharma, Inc. v. FDA*, 119 F. Supp. 3d 196, 199 (S.D.N.Y. 2015) (four medical doctors joined with the pharmaceutical company Amarin in suing the FDA); *see also Sorrell v. IMS Health Inc.*, 564 U.S. 552, 578 (2011) (noting that doctors find detailing “very helpful”).

169. *Amarin Pharma*, 119 F. Supp. 3d at 213 (alleging that FDA rules operate “to keep doctors . . . in the dark about all the options for drug therapy they are legally empowered to prescribe” (quoting paragraphs 8–9 of the Complaint)).

170. *See* David Strang, Micheline Gagnon, William Molloy, Michel Bédard, Peteris Darzins, Edward Etchells & Warren Davidson, *National Survey on the Attitudes of Canadian Physicians Towards Drug-Detailing by Pharmaceutical Representatives*, 29 ANNALS ROYAL C. PHYSICIANS & SURGEONS CAN. 474 (1996) (finding that eighty percent of doctors agree that detailing overstates drug effectiveness). The reality is that detailing tends to be incomplete. *See* Barbara Mintzes, Joel Lexchin, Jason M. Sutherland, Marie Dominique Beaulieu, Michael S. Wilkes, Geneviève Durrieu & Ellen Reynolds, *Pharmaceutical Sales Representatives and Patient Safety: A Comparative Prospective Study of Information Quality in Canada, France and the United States*, 28 J. GEN. INTERNAL MED. 1368, 1374 (2013).

171. *E.g.*, Elisabeth H. Creyer & Ilias Hrsistodoulakis, *Marketing Pharmaceutical Products to Physicians: Sales Reps Influence Physicians Impressions of the Industry*, MARKETING HEALTH SERVS., Summer 1998, 34, 36–38 (noting that sales representatives are a key source of information and that fifty-five percent of residents surveyed believed information was accurate, even though less than half considered representatives to be trustworthy); Lisa D. Spiller & Walter W. Wymer, Jr., *Physicians’ Perceptions and Uses of Commercial Drug Information Sources: An Examination of Pharmaceutical Marketing to Physicians*, 19 HEALTH MARKETING Q. 91, 97 (2001) (finding that a vast majority of physicians considered the visits “somewhat helpful,” with nearly twenty percent considering the visits “extremely helpful”); Michael G. Ziegler, Pauline Lew & Brian C. Singer, *The Accuracy of Drug Information from Pharmaceutical Sales Representatives*, 273 J. AM. MED. ASS’N, 1296, 1298 (1995) (noting that seventy-four percent of residents found pharmaceutical representative information to be useful); *see also* HOUSE OF COMMONS: HEALTH COMM., THE

prescription behavior is not influenced by detailing and claim that they are able to critically evaluate information from sales representatives;<sup>172</sup> although some doctors realize that there may be some influence.<sup>173</sup> However, in general, doctors believe only *other* doctors are susceptible.<sup>174</sup> This is an apt example of the overconfidence

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INFLUENCE OF THE PHARMACEUTICAL INDUSTRY, 2004–05, HC 42-II, at 64 (UK) (criticizing doctors for uncritically relying on industry information); Helen Prosser, Solomon Almond & Tom Walley, *Influences on GPs' Decision to Prescribe New Drugs – The Importance of Who Says What*, 20 FAM. PRAC. 61, 64 (2003) (noting that seventy percent of UK doctors considered sales representatives an efficient way of obtaining information about drug information).

172. See Freek Fickweiler, Ward Fickweiler & Ewout Urbach, *Interactions Between Physicians and the Pharmaceutical Industry Generally and Sales Representatives Specifically and Their Association with Physicians' Attitudes and Prescribing Habits: A Systematic Review*, 7 BRIT. MED. J. OPEN 1, 3 (2017) (noting that a majority of studies found that doctors do not believe interactions with industry reps had any impact on prescription behavior); Melissa A. Fischer, Mary Ellen Keough, Joann L. Baril, Laura Saccoccio, Kathleen M. Mazor, Elissa Ladd, Ann Von Worley & Jerry H. Gurwitz, *Prescribers and Pharmaceutical Representatives: Why Are We Still Meeting?*, 24 J. GEN. INTERNAL MED. 795, 796 (2009) (finding that although most doctors recognized that there were studies indicating the influence of detailing on prescriptions, they nonetheless believed that they were not unduly influenced, with some asserting that they were able to adequately glean useful information from the marketing). The same phenomena is seen with doctors in other countries. *E.g.*, Prosser et al., *supra* note 171, at 64 (noting that general practitioners in the UK felt able to separate credible from misleading information, even though they generally questioned the objectivity of the industry); Aldo De Ferrari, Cesar Gentile, Long Davalos, Leandro Huayanay & German Malaga, *Attitudes and Relationship Between Physicians and the Pharmaceutical Industry in a Public General Hospital in Lima, Peru*, PLOS ONE, June 2014, at 3 (noting that almost ninety percent of doctors in Peru assumed gifts and free lunches had no impact on prescribing behavior); Mário César Scheffer, *Interactions Between Pharmaceutical Companies and Physicians Who Prescribe Antiretroviral Drugs for Treating AIDS*, 132 SAO PAULO MED. J. 55, 58 (2014) (noting that forty percent of doctors in Brazil claimed that interactions with representatives had no influence whatsoever on their prescriptions).

173. Fickweiler et al., *supra* note 172, at 3 (noting studies where some doctors admit possible influence of pharmaceutical detailing); *see also* Klaus Lieb & Armin Scheurich, *Contact Between Doctors and the Pharmaceutical Industry, Their Perceptions and the Effects on Prescribing Habits*, PLOS ONE, Oct. 2014, at 3 (finding forty-two percent of German doctors believed their prescribing habits were influenced).

174. John A. Hopper, Mark W. Speece & Joseph L. Musial, *Effects of an Educational Intervention on Residents' Knowledge and Attitudes Toward Interactions with Pharmaceutical Representatives*, 12 J. GEN. INTERNAL MED. 639, 641 (1997) (doctors strongly disagreed that interactions with pharma representatives would influence their own prescription behavior, but assumed that most other doctors would be susceptible); M. A. Morgan, J. Dana, G. Loewenstein, S. Zinberg & J. Schulkin, *Interactions of Doctors with the Pharmaceutical Industry*, 32 J. MED. ETHICS 559 (2006) (most OB-GYN doctors surveyed believed that others would be more likely to be influenced); Michael A. Steinman, Michael G. Shlipak & Stephen J. McPhee, *Of Principles and Pens*, 110 AM. J. MED. 551 (2001) (finding that sixty-one percent of internal medicine residents claimed that promotions, such as gifts, had no impact on them, but only sixteen percent thought this was true of other doctors). However, how questions are phrased in studies may get different results. Stephen K. Sigworth, Mary D. Nettleman & Gail M. Cohen, *Pharmaceutical Branding of Resident Physicians*, 286 J. AM MED. ASS'N 1024, 1025 (2001) (finding over ninety percent of residents admitted that detailing had “some

bias in action, as studies indicate doctors are in fact influenced by pharmaceutical marketing, as discussed in the next section.

The sophisticated doctor schema is also consistent with the fact that doctors strongly value their clinical autonomy. In fact, the FDA's current circuitous attempt to regulate off-label use of drugs may be a reaction to physician opposition to more direct regulation. For example, in the 1960s, the FDA was reportedly criticized by the medical community when the FDA asked the author of a medical textbook to warn against unsafe dosage of a product that resulted in several deaths.<sup>175</sup> Physician opposition to adding information about dangerous dosages of a product is consistent with doctors holding a schema that they do not need information from someone outside their profession about dangers of a drug. This schema is consistent with a general culture of resisting perceived intrusions on independent professional judgments, with some suggesting that medical training and professional orientation make them wary of ceding clinical discretion to a nonphysician.<sup>176</sup> Some studies note that initial medical training has a long-term impact and that disregard of evidence-based information may be a function of their experience during residency where the attending physician's opinion was considered all-important over other information sources.<sup>177</sup>

The sophisticated doctor schema may also result in some doctors valuing their own clinical experience over data in peer review publications. Studies indicate that doctors consider their own clinical experience very important in deciding what to prescribe.<sup>178</sup> Some studies indicate that doctors not only express disbelief about scientific studies that contradict their perceived clinical practice, but also express a strong belief that their clinical experience is superior.<sup>179</sup> In other words, the

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influence").

175. Klasmeier & Redish, *supra* note 5, at 321.

176. *E.g.*, Mark A. Hall, *Institutional Control of Physician Behavior: Legal Barriers to Health Care Cost Containment*, 137 U. PA. L. REV. 431, 451, 462–63 (1988); *see also* James L. Reinersten, *Zen and the Art of Physician Autonomy Maintenance*, 138 ANNALS INTERNAL MED. 992 (2003) (noting common physician objections to guidelines).

177. Johnson, *supra* note 22, at 76–77 (citing Stefan Timmermans & Alison Angell, *Evidence Based Medicine, Clinical Uncertainty, and Learning to Doctor*, 42 J. HEALTH & SOC. BEHAV. 342, 345–47 (2001)).

178. Jerry Avorn, Milton Chen & Robert Hartley, *Scientific Versus Commercial Sources of Influence on Prescribing Behavior of Physicians*, 73 AM. J. MED. 4 (1982) (noting that eighty-eight percent of doctors considered their own experience very important and more important than scientific papers or other sources); *see also* Niteesh K. Choudhry, Robert H. Fletcher & Stephen B. Soumerai *Systematic Review: The Relationship between Clinical Experience and Quality of Health Care*, 142 ANNALS OF INTERNAL MED. 260, 262–63 (2005) (finding that doctors relied on their own beliefs rather than empirical studies or guidelines by institutions such as the National Cancer Institute).

179. Rebecca K. Schwartz, Stephen B. Soumerai & Jerry Avorn, *Physician Motivations for Nonscientific Drug Prescribing*, 28 SOC. SCI. & MED. 577, 579 (1989) (noting that doctors claim that their “‘real-world medicine,’ was more relevant to clinical practice than academic studies”); *see also* Narcyz Ghinea, Ian Kerridge, Miles Little & Wendy Lipworth, *Challenges to the Validity of Using Medicine Labels to Categorize Clinical Behavior: An Empirical and Normative Critique of “Off-Label” Prescribing*, 23 J. EVALUATION CLINICAL PRAC. 574, 577 (2017) (noting that doctors are skeptical that regulatory approval is more meaningful than their



sophisticated doctor schema not only makes doctors believe they are invulnerable to commercial marketing, but also that their experience is more valuable than scientific evidence. Understanding this helps to explain why doctors are resistant to changing their practices in light of scientific evidence. For example, one study shows that it takes from ten to twenty years of evidence before there is widespread adoption of scientifically supported clinical changes,<sup>180</sup> and doctors are often resistant to adopting guidelines from organizations such as the National Cancer Institute or the National Cholesterol Education Program.<sup>181</sup> In extreme cases, doctors sometimes continue with medical practices that studies have affirmatively shown to be inferior.<sup>182</sup> This resistance could be a result of the same sophisticated doctor schema. Of course, for the purpose of this discussion, doctors in general are considered to all share this trait, although there are some differences by age and gender.<sup>183</sup>

In addition, legal academics may also indulge in the sophisticated doctor bias. For example, one First Amendment scholar argued that if doctors often prescribe medicine for off-label use

[i]t cannot be that doctors do not know what they are doing, do not care for their patients, or have somehow been seduced or suckered by drug companies . . . . The most *plausible* intuitive answer . . . is that doctors . . . have made the independent, professional medical judgment that the

own clinical opinion since countries are not consistent in approval of the same drugs). This is consistent with the overconfidence cognitive bias.

180. E. A. Balas & S. A. Boren, *Managing Clinical Knowledge for Health Care Improvement*, Y.B. MED. INFORMATICS, 2000, at 66 (noting that it requires seventeen years for research evidence to result in clinical changes and ten years before treatment recommendations for new therapies appear in medical textbooks).

181. John A. Sbarbaro, *Can We Influence Prescribing Patterns?*, 33 CLINICAL INFECTIOUS DISEASES S240, S241 (2001).

182. For example, in 2007, after an influential medical journal published research showing that the then-common procedure of heart surgery using stents to unclog blocked arteries was no more effective than drugs alone, although the stent procedure briefly declined, it began to increase again. Keith J. Winstein, *A Simple Health-Care Fix Fizzles Out*, WALL ST. J. (Feb. 11, 2010, 1:26 PM), <https://www.wsj.com/articles/SB10001424052748703652104574652401818092212?ns=prod/accounts-wsj> [<https://perma.cc/MZ49-VLX2>]. Of course, the doctor resistance in this case may be linked to an issue not present with drug prescription—a higher level of reimbursement for a procedure rather than drugs alone. However, doctors seem to generally resist changing practices long after empirical data shows the need to do so. Aaron E. Carroll, *It's Hard for Doctors to Unlearn Things. That's Costly for All of Us*, N.Y. TIMES: UPSHOT (Sept. 10, 2018), <https://www.nytimes.com/2018/09/10/upshot/its-hard-for-doctors-to-unlearn-things-thats-costly-for-all-of-us.html> [<https://perma.cc/VZE2-8F3K>] (discussing a study indicating that doctors continue to use procedures even after they have been proved ineffective).

183. Jette V. Le, Line B. Pedersen, Helle Riisgaard, Jesper Lykkegaard, Jørgen Nexøe, Jeannette Lemmergaard & Jens Søndergaard, *Variation in General Practitioners' Information-Seeking Behaviour – A Cross-Sectional Study on the Influence of Gender, Age and Practice Form*, 34 SCANDINAVIAN J. PRIMARY HEALTH CARE 327, 328 (2016) (finding female and younger physicians more likely to know about and adhere to guidelines).

prescription, on balance, holds more promise of doing good for the patient than harm.<sup>184</sup>

This may sound intuitive, but it is an intuition that may not be actually supported, as the next Section shows. Of course, other legal academics have recognized that doctors are not so sophisticated, although without recognizing the existence of an overarching schema.<sup>185</sup>

## 2. Debunking the Sophisticated Doctor Schema

This Section provides evidence to contradict the sophisticated doctor schema held by judges, academics, and even doctors themselves. This Section begins by showing that a substantial number of doctors are actually *not* sophisticated regarding their knowledge of approved uses of drugs—even though they consider what uses are approved to be important. Not only does this support the existence of a misplaced sophisticated doctor schema, but it has implications for doctors' vulnerability to marketing they may assume is for on-label, as opposed to off-label use. Then, this Section builds upon the fact that doctors are not sophisticated about what is an approved use of a drug to show why doctors are far more vulnerable to marketing influences than they realize.

In evaluating whether doctors are able to cull out valid information from self-interested promotion about off-label uses that have not been reviewed by the FDA for accuracy (which the sophisticated doctor schema assumes is possible), a helpful starting point is the extent to which doctors are knowledgeable about *approved* uses. After all, if a doctor cannot readily distinguish which uses are approved, it will be more difficult for a doctor to identify when marketing focuses on unapproved uses and to be more suspect of such information. Unfortunately, a substantial number of doctors are confused about approved uses, even though they consider this to be an important factor regarding what drugs to prescribe. A 2009 study found that a significant number of doctors falsely believed some drugs uses were FDA approved in situations that the FDA had warned against.<sup>186</sup> In other words, a substantial number

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184. Smolla, *supra* note 5, at 87; *see also* Bagley et al., *supra* note 7, at 386 (arguing that doctors are sophisticated consumers as noted in *Sorrell* and thus arguably there can be no harm to any “scientific” information provided by industry representatives); Thea Cohen, *The First Amendment and the Regulation of Pharmaceutical Marketing: Challenges to the Constitutionality of the FDA’s Interpretation of the Food, Drug, and Cosmetics Act*, 49 AM. CRIM. L. REV. 1945, 1967 (2012) (noting that there is trust in prescribers to make “life or death decisions” and be able to “evaluate health-related information, whatever its source”).

185. *E.g.*, Stephanie M. Greene, Debate, *FDA Prohibitions on Off-Label Marketing Do Not Violate Drug Manufacturers’ First Amendment Rights*, 162 U. PA. L. REV. ONLINE 239, 243 (2014) (stating that courts have mistakenly assumed that doctors are able to discern misleading from nonmisleading information, citing the *Sorrell* court’s reference to doctors as “sophisticated” in particular, even though that is contrary to literature showing doctors learn about products primarily from the industry); *see also* Jonathan J. Darrow, *Pharmaceutical Gatekeepers*, 47 IND. L. REV. 363, 368–69 (2014) (noting that doctors rely on company information and often assume new drugs are better).

186. Donna T. Chen, Matthew K. Wynia, Rachael M. Moloney & G. Caleb Alexander, *U.S. Physician Knowledge of the FDA-Approved Indications and Evidence Base for*

of doctors were fundamentally confused on what was FDA approved, even when they considered this to be relevant and important information. Similar findings have been reported in studies in other countries.<sup>187</sup>

Troublingly, doctors have been found to conflate warnings *against* a use with the assumption that the use has actually been approved. For example, in the same 2009 study, one-third of doctors thought that a drug was approved for chronic anxiety when in fact the FDA had warned *against* this use, which could reflect conflation of off-label marketing of the drug for such use with a “black box” warning on the label,<sup>188</sup> although this particular study did not focus on that issue.<sup>189</sup> Similarly, nearly one in five doctors prescribed a drug for what they thought was an FDA-approved use, when in fact at the time of the survey, that use had a black box warning for increased risk of *death*.<sup>190</sup> This experimental finding about black box warning confusion is not an isolated incident; there are other situations where black box warnings do not appear to limit use, and sometimes use seems to increase—even after a manufacturer sends a letter directly to doctors.<sup>191</sup> Doctors could be unaware

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*Commonly Prescribed Drugs: Results of a National Survey*, 18 PHARMACOEPIDEMOLOGY & DRUG SAFETY 1094, 1098 (2009) (finding that nineteen percent of doctors prescribed Seroquel for dementia with agitation believing it was FDA approved for such use when in fact the FDA required a black box warning for use in elderly patients, and over seventy percent of doctors prescribed lorazepam to treat chronic anxiety assuming it was approved for this use when in fact the FDA warned against such use).

187. *E.g.*, Ghinea et al., *supra* note 179, at 576 (stating that Australian doctors are often unaware they are prescribing off label or even what that means); Constans C. A. H. H. V. M. Verhagen, Anne G. H. Niezink, Yvonne Y. Engels, Yechiel Y. A. Hekster, Joan J. Doornebal & Kris C. P. Vissers, *Off-Label Use of Drugs in Pain Medicine and Palliative Care: An Algorithm for the Assessment of Its Safe and Legal Prescription*, 8 PAIN PRAC. 157, 158 (2008) (finding that staff members in the Netherlands were not always aware they were prescribing pain medication off label).

188. Chen et al., *supra* note 186, at 1098. This is the most severe warning that appears on approved drugs and appears in a box on the label to warn of serious health risks, including health-threatening risks. 21 C.F.R. § 201.57(c)(1) (2018) (noting a boxed warning may be appropriate for serious warnings and “particularly those that may lead to death or serious injury” and is usually based on clinical data); *see also* Judith E. Beach, Gerald A. Faich, F. Gail Bormel & Frank J. Sasinowski, *Black Box Warnings in Prescription Drug Labeling: Results of a Survey of 206 Drugs*, 53 FOOD & DRUG L.J. 403, 405–08 (1998) (stating that although the FDA has not clearly indicated bases for black box warnings, empirical data concerning situations in which black box warnings are provided fall into six categories, primarily focused on high-risk patients and are generally based on clinical studies submitted as part of new drug applications, but possibly from postmarket reporting or epidemiological surveys); Shirley Murphy & Rosemary Roberts, “Black Box” 101: *How the Food and Drug Administration Evaluates, Communicates, and Manages Drug Benefit/Risk*, 117 J. ALLERGY & CLINICAL IMMUNOLOGY 34 (2006).

189. Chen et al., *supra* note 186, at 1098.

190. *Id.*

191. *E.g.*, Walter Smalley, Deborah Shatin, Diane K. Wysowski, Jerry Gurwitz, Susan E. Andrade, Michael Goodman, K. Arnold Chan, Richard Platt, Stephanie D. Schech & Wayne A. Ray, *Contraindicated Use of Cisapride: Impact of Food and Drug Administration Regulatory Action*, 284 J. AM. MED. ASS’N 3036, 3036–37 (2000). The public health problem only terminated after the manufacturer voluntarily withdrew the product from market on the

of black box warnings,<sup>192</sup> but other studies suggest that doctors are aware of such warnings and simply do not follow them.<sup>193</sup> So, even rigorous FDA efforts to warn doctors about drug risks may have less impact than commercial marketing.<sup>194</sup>

The sophisticated doctor schema is also well illustrated by a key 1982 study that reveals doctors are much more influenced by commercial rather than scientific sources.<sup>195</sup> The study chose two drugs for which there was substantial scientific literature showing that the drugs were not effective,<sup>196</sup> or at least no better than over-the-counter options, and interviewed a random sample of primary care physicians.<sup>197</sup> Given this, questions about the perceived value of these drugs that correlate with commercial promotion could appropriately link actual impact of commercial forces. A substantial majority (sixty-two percent) stated that academic sources were “very important” in shaping their decisions and a majority similarly claimed commercial sources to be of “minimal importance.”<sup>198</sup> However, responses regarding scientifically unsupported statements touted by the industry indicate more commercial influence than doctors reported. For example, nearly half of doctors thought one drug, propoxyphene, was more potent than aspirin, contrary to scientific

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eve of an FDA review of the drug’s benefit versus risks, as well as after eighty reported deaths. Gardiner Harris & Eric Koli, *Lucrative Drug, Danger Signals and the F.D.A.*, N.Y. TIMES (June 10, 2005), <http://www.nytimes.com/2005/06/10/business/lucrative-drug-danger-signals-and-the-fda.html> [<https://perma.cc/7Z7E-ZZ2Z>]; Sheryl Gay Stolberg, *Heartburn Drug Linked to Deaths to Be Withdrawn*, N.Y. TIMES (Mar. 24, 2000), <http://www.nytimes.com/2000/03/24/us/heartburn-drug-linked-to-deaths-to-be-withdrawn.html> [<https://perma.cc/J5FD-DVRC>].

192. Larkin et al., *Restrictions*, *supra* note 64, at 1021 (suggesting a lack of awareness of FDA-approved indications for psychiatric drugs, as well as black box warnings as possible explanations for significant increase in off-label prescribing of some drugs after detailing was limited).

193. See Supriya K. Bhatia, Amy J. Rezac, Benedetto Vitiello, Michael A. Sitorius, Bruce A. Buehler & Christopher J. Kratochvil, *Antidepressant Prescribing Practices for the Treatment of Children and Adolescents*, 18 J. CHILD & ADOLESCENT PSYCHOPHARMACOLOGY 70, 73–75 (2008) (finding that nearly ninety-seven percent of surveyed psychiatrists were aware of black box warnings relating to antidepressants for children, but few adhered to the FDA guidelines).

194. The persistence of the sophisticated doctor schema may be reinforced by other cognitive biases. For example, the overconfidence bias likely makes doctors assume they are not vulnerable to marketing. In addition, the availability bias may make doctors rely more on information that is most repeated (i.e., commercial marketing).

195. Avorn et al., *supra* note 178, at 7.

196. One drug was a vasodilator widely promoted for senile dementia contrary to clinical literature showing lack of utility, whereas the other drug, propoxyphene, was promoted for severe pain even though more than eight studies showed no advantage over a placebo. *Id.* at 4–5.

197. Although the sample was randomly chosen among doctors in Boston who listed internal medicine or general medicine as their area of practice, two-thirds were solo practitioners, who in other studies seem to be more influenced by commercial marketing since they do not have readily accessible colleagues. *Id.* at 5.

198. Drug advertising was considered of minimal importance to sixty-eight percent and drug representative visits were of minimal importance to fifty-four percent. *Id.* Less than thirty percent considered each to be of moderate importance. *Id.*

data, yet consistent with commercial promotion.<sup>199</sup> Similarly, almost half thought that vasodilators were effective for senile dementia, which is consistent with advertising, but inconsistent with actual scientific literature.<sup>200</sup> Accordingly, this study indicates that doctors are substantially impacted by commercial sources, even if the sources actually contradict what scientific studies report, contrary to doctors' claims that they value scientific studies more.<sup>201</sup> The study did not look at actual prescription data, but national prescribing data on these drugs are consistent with the study (i.e., the drugs are overprescribed relative to their actual utility).<sup>202</sup>

A follow-up study in 1989 by one of the same authors as the 1982 study similarly debunks the sophisticated doctor schema. The 1989 study involved the same drugs as the original study, as well as one additional drug; this second study yielded similar data.<sup>203</sup> Although doctors were not specifically asked about reliance on commercial sources, more than a quarter of statements made by doctors in interviews contradicted the scientific literature, but mirrored commercial promotions.<sup>204</sup> Moreover, when confronted about the discrepancy, some doctors rejected the scientific data; one doctor claimed clinical experience was more relevant than academic studies and others asserted that their own "studies" prove the opposite.<sup>205</sup> In other words, although doctors assume that they are highly sophisticated in discerning accurate information from promotions, not only are they vulnerable to these promotions, but they also do not realize it.

A related problem is that, contrary to court assumptions that doctors are sophisticated enough to evaluate peer review articles presented by self-interested companies, the reality is likely different. First, although doctors are trained in

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199. *Id.*

200. *Id.*; see also Schwartz et al., *supra* note 179, at 579 (finding that twenty-six percent of doctors claimed therapeutic advantages of vasodilators on senile dementia, as well as the benefit of propoxyphene, despite a lack of scientific support).

201. One small caveat is that although doctors generally dismissed patient preferences as not relevant to their prescriptions, answers to some questions suggest that they were influenced. See Avorn et al., *supra* note 178, at 6 (stating that over eighty percent of doctors stated that they "often" prescribe a drug for pain because patients were not satisfied with over-the-counter drugs); see also J. Gambrill & C. Bridges-Webb, *Use of Sources of Therapeutic and Prescribing Information by General Practitioners*, 9 AUSTL. FAM. PHYSICIAN 482, 483 (1980) (noting that doctors reported journals as the most useful source for prescribing, with sales representatives listed second). *But see* Donald P. Connelly, Eugene C. Rich, Shawn P. Curley & John T. Kelly, *Knowledge Resource Preferences of Family Physicians*, 30 J. FAM. PRAC. 352, 356-59 (1990) (finding that family physicians reported scientific articles to be not credible or accessible, albeit based on self-reported data).

202. See Avorn et al., *supra* note 178, at 7.

203. Schwartz et al., *supra* note 179, at 578. The study focused on possible interventions—one involving a mailing of a visually appealing "un-advertisement" including scientific and economic costs and benefits to prescribing the scientifically unsupported drugs, whereas the other involved the same mailing as well as a visit by a pharmacist to educate doctors about the drugs, suggest practical alternatives, and answer questions. The mailing group did not reduce prescriptions significantly, whereas the group that was visited in-person reduced prescription of the studied drugs by fourteen percent. *Id.*

204. See *id.* at 579.

205. *Id.*

science, as busy individuals, they often do not read more than abstracts, which have been found to be inaccurate.<sup>206</sup> In addition, not only is there a general publication bias on positive outcomes, but companies will selectively present only favorable articles to doctors,<sup>207</sup> which sometimes have been “ghostwritten” by the industry.<sup>208</sup> Although doctors should know that they are only presented with selective information, they may not actually be capable of processing that biased information. Notably, one study found that when doctors were presented with a study that reported the positive results of a drug based on only one of the five trials conducted, they were more likely to prescribe the drug, even without being given the other data, let alone an opportunity to evaluate its veracity.<sup>209</sup> In addition, once doctors have been influenced by the industry, it may be difficult to change their behavior. For example, after many articles touted off-label use of a coagulant, more than ninety-seven percent of prescriptions were made for such uses—even after a systematic review concluded that off-label use was unwarranted.<sup>210</sup>

Although doctors realize that the goal of sales representatives is to promote sales, they do not seem as sophisticated as courts and some scholars assume in evaluating such information. They seem unaware of what information is reliable. For example, some doctors improperly assume that detailing is more reliable than printed advertising.<sup>211</sup> However, in reality, advertisements are regulated by the FDA whereas sales representatives are generally not regulated, and they have been found to provide false or misleading statements in detailing.<sup>212</sup> In addition, although studies have

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206. See Sanjay Saint, Dimitri A. Christakis, Somnath Saha, Joann G. Elmore, Deborah E. Welsh, Paul Baker & Thomas D. Koepsell, *Journal Reading Habits of Internists*, 15 J. GEN. INTERNAL MED. 881, 883 (2000). Another, but slightly different, problem is that abstracts do not disclose potential conflicts of interest, which could put a doctor on notice that a study was funded by a self-interested company. See Céline Buffel du Vaure, Isabelle Boutron, Elodie Perrodeau & Philippe Ravaud, *Reporting Funding Source or Conflict of Interest in Abstracts of Randomized Controlled Trials, No Evidence of a Large Impact on General Practitioners' Confidence in Conclusions, a Three-Arm Randomized Controlled Trial*, BIOMED CENT. MED., 2014, at 2.

207. *E.g.*, Wash. Legal Found. v. Friedman, 13 F. Supp. 2d 51, 65 (D.D.C. 1998).

208. Essentially, the industry hires freelance writers to provide a draft to a sham academic author to publish, and journals are generally not aware of the problem since the author will not disclose any conflict of interest. See Marcia Angell, *Industry-Sponsored Clinical Research: A Broken System*, 300 J. AM. MED. ASS'N 1069 (2008); Jeffrey R. Lacasse & Jonathan Leo, *Ghostwriting at Elite Academic Medical Centers in the United States*, PLOS MED., Feb. 2010, at 1; Joseph S. Wislar, Annette Flanagan, Phil B. Fontanarosa & Catherine D. DeAngelis, *Honorary and Ghost Authorship in High Impact Biomedical Journals: A Cross Sectional Survey*, 343 BRIT. MED. J. 1192 (2011). Natasha Singer, *Medical Papers by Ghostwriters Pushed Therapy*, N.Y. TIMES (Aug. 4, 2009), <https://www.nytimes.com/2009/08/05/health/research/05ghost.html> [<https://perma.cc/U3WS-9QDQ>].

209. Gabriel K. Silverman, George F. Loewenstein, Britta L. Anderson, Peter A. Ubel, Stanley Zinberg & Jay Schulkin, *Failure to Discount for Conflict of Interest When Evaluating Medical Literature: A Randomised Trial of Physicians*, 36 J. MED. ETHICS 265, 267 (2010).

210. N. Ghinea, W. Lipworth, I. Kerridge & R. Day, *No Evidence or No Alternative? Taking Responsibility for Off-Label Prescribing*, 42 INTERNAL MED. J. 247, 248 (2012).

211. Ziegler et al., *supra* note 171, at 1297–98.

212. 21 C.F.R. § 202.1 (2017); Beth Synder Bulik, *Pharma Sales Rep Regulations*

shown that detailing tends to exclude negative information,<sup>213</sup> doctors sometimes erroneously believe that negative effects are disclosed by detailers.<sup>214</sup> The most extreme example of lack of physician sophistication in evaluating detailing information is from a study that found that doctors are often unable to discern false statements from drug representatives.<sup>215</sup> The representatives made statements that were contradicted by readily available sources, including company literature, as well as the *Physician's Desk Reference*, despite the fact that the study involved the unique situation where drug representatives knew that their statements were actually being recorded.<sup>216</sup> Improbable claims also went unchallenged.<sup>217</sup> Of particular concern, two false statements were not only undetected, but would result in dangerous outcomes if accepted at face value. For example, one statement claimed that there was no need to monitor for hematologic side effects, *contrary* to the package insert with a boxed warning.<sup>218</sup>

Even doctors who are skeptical about whether industry information is accurate may nonetheless rely on inaccurate information due to the cognitive bias of accessibility. For example, since company detailing is more readily available and easier to process than scientific articles, studies showing that doctors consider detailing more “valuable” than scientific articles, even if less credible, should not be surprising. Along similar lines, advertising may have more of an impact than peer reviewed articles on prescriptions because it is similarly more accessible.<sup>219</sup> This seems to be consistent with the 1982 study that indicates doctors were more influenced by commercial sources than scientific sources with respect to scientifically discredited drugs. In particular, it could be that doctors believe that they should be influenced more by academic than commercial sources, but in reality, commercial sources are more accessible and thus more influential.

### C. The More Information Schema

This Section explains the schema in commercial speech cases that favors more information and why several long-standing principles in the law are not supported

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*Proposal Stalls in Philadelphia, but the Battle's Not over Yet*, FIERCEPHARMA (Jan. 7, 2019, 9:07 AM), <https://www.fiercepharma.com/marketing/sales-rep-regulations-proposal-stalls-philly-but-city-vs-pharma-not-over-yet> [<https://perma.cc/5HAH-AS5A>] (noting a failure to pass legislation in Philadelphia that would require regulation of sales representatives, and only Chicago and the state of Nevada have passed this type of legislation thus far); *see also supra* note 50 (discussing misrepresentations that have contributed to the opioid epidemic); *infra* note 283 (discussing misrepresentations made by sales representative in the *Caronia* case).

213. *E.g.*, *Sales Representatives: A Damning Report by Prescribe Reps Monitoring Network*, 8 PRESCRIBE INT'L 86 (1999).

214. *See* Strang et al., *supra* note 170, at 476.

215. Ziegler et al., *supra* note 171, at 1297.

216. *Id.* at 1296, 1298.

217. *Id.* at 1298.

218. *Id.* at 1297.

219. *See* Pierre Azoulay, *Do Pharmaceutical Sales Respond to Scientific Evidence?*, 11 J. ECON. & MGMT. STRATEGY 551, 586 (2002) (finding that, in a study of H2 blockers, although scientific studies had some impact, marketing and especially detailing had a pronounced effect).

by empirical data. In particular, it shows how courts have relied on this schema to favor and expand commercial speech in three ways. First, courts require a high burden of proof for allegedly misleading information. Second, courts treat potentially misleading information as legally interchangeable with true information. Third, courts presume disclaimers will alleviate confusion or deception. However, this Section explains that empirical studies do not support these current commercial speech hallmarks.

### 1. What Is the More Information Schema?

The more information schema is deeply embedded in commercial speech case law that generally favors permitting commercial speech. As discussed earlier, commercial speech case law prefers permitting information over suppression since it is presumed to provide valuable information to the audience that will promote informed decisions. The *Washington Legal Foundation* district court noted that “[i]f there is one fixed principle in the commercial speech arena, it is that ‘a State’s paternalistic assumption that the public will use truthful, nonmisleading commercial information unwisely cannot justify a decision to suppress it,’”<sup>220</sup> and any such restriction is “practically an engraved invitation to have the restriction struck.”<sup>221</sup> This preference towards more information has been consistent from the first Supreme Court case to clearly hold commercial speech entitled to First Amendment protection. In that first case, the Court stated that “people will perceive their own best interests if only they are well enough informed, and that the best means to that end is to *open* the channels of communication rather than to close them,”<sup>222</sup> which many subsequent courts have cited.<sup>223</sup>

The more information schema also supports the current high burden of proof on establishing that commercial speech is inherently misleading to permit it to be absolutely barred without consideration of any other factors. For example, in *Washington Legal Foundation*, the court rejected the suggestion that scientific claims are presumptively misleading unless approved by the FDA, which seems consistent with the more information schema.<sup>224</sup> As will be explained, scientific claims made even in peer review journals are likely to be misleading and potentially even false. Along similar lines, one court rejected the FDA’s assertion that commercial claims regarding supplements are inherently confusing when not supported by substantial scientific evidence; the FDA’s contention was characterized as “almost frivolous,”

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220. *Wash. Legal Found. v. Friedman*, 13 F. Supp. 2d 51, 69–70 (D.D.C. 1998) (quoting 44 *Liquormart, Inc. v. Rhode Island*, 517 U.S. 484, 497 (1996)).

221. *Id.* at 70.

222. *Va. State Bd. of Pharmacy v. Va. Citizens Consumer Council*, 425 U.S. 748, 770 (1976) (emphasis added); *see also id.* at 765 (stating that the goal of commercial speech is to ensure that decisions are “intelligent and well informed” and that promoting “the free flow of commercial information is indispensable”).

223. *E.g.*, *Liquormart*, 517 U.S. at 497; *Bolger v. Youngs Drug Prods. Corp.*, 463 U.S. 60, 79 (1983); *Cent. Hudson Gas & Elec. Corp. v. Pub. Serv. Comm’n of N.Y.*, 447 U.S. 557, 562 (1980); *Am. Acad. of Implant Dentistry v. Parker*, 152 F. Supp. 3d 641, 651 (W.D. Tex. 2016); *Whitaker v. Thompson*, 248 F. Supp. 2d 1, 8 (D.D.C. 2002).

224. *Wash. Legal Found.*, 13 F. Supp. 2d at 67.



and the court analogized the FDA claim to suggesting consumers would be hypnotized to buy a product.<sup>225</sup>

In addition, the more information schema supports the current law that treats potentially misleading information identically to truthful information that is clearly not misleading. Notably, although courts consistently recognize harms from actually misleading information, it seems questionable to assume that potentially misleading information is not harmful. Admittedly, the difference in treatment is largely a reflection of the fact that some information can be entirely barred due to harms, even without full consideration of all *Central Hudson* factors. However, treating potentially misleading information as legally equivalent to information that is completely truthful and not misleading seems to rely on the assumption that more information—even if potentially misleading—is preferable. The more information schema assumes that additional information from another source will correct any information flaws. However, as noted earlier, that is not likely in the context of marketing of pharmaceutical drugs for which the marketplace is one sided.

The more information schema also explains court views on disclaimers and clarifications in the context of commercial speech decisions. In particular, courts often reject government assertions that commercial speech will be potentially misleading based on the assumption that a less restrictive—and presumed effective—alternative would be a disclaimer or warning concerning information that is considered misleading.<sup>226</sup> For example, in *Washington Legal Foundation*, even though the court noted that a company would selectively provide only favorable peer review publications to doctors with potential to mislead,<sup>227</sup> the court dismissed concerns that this could be potentially misleading for physicians and stated that the documents could have “conspicuous notifications” that the use being discussed was not approved.<sup>228</sup> In one extreme situation, a court assumed a disclaimer is not confusing unless there is empirical evidence of such a fact.<sup>229</sup> However, as the next Section will establish, this presumption concerning disclaimers is contrary to empirical evidence.

## 2. Evidence Debunking “More Information Is Better” Schema

This Section provides empirical evidence to contradict the seemingly logical presumption that more information provides more informed results. Consistent with the earlier discussion of cognitive limits, this Section explains that there are serious cognitive limits to processing disclaimers, which is very important to the popular

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225. *Pearson v. Shalala*, 164 F.3d 650, 655 (D.C. Cir. 1999); *see also* *Int’l Dairy Foods Ass’n v. Boggs*, 622 F.3d 628, 636–37, 639 (6th Cir. 2010) (relying on amici information and discounting the FDA view that a statement that milk from cows not treated with hormone might improperly suggest milk is safer and asserting that any possible problem with misleading claims is alleviated by a disclaimer).

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

227. *Wash. Legal Found.*, 13 F. Supp. 2d at 65 (stating this in the context of concluding that distribution of scientific articles constitutes commercial speech, rather than scientific and academic speech that is deserving of more First Amendment protection).

228. *Id.* at 68.

229. *Whitaker v. Thompson*, 248 F. Supp. 2d 1, 13 (D.D.C. 2002).

First Amendment solution of providing disclaimers as a less speech restrictive means that allegedly will protect against misleading information.<sup>230</sup> Although there are no known studies of disclaimers regarding off-label drug use, there are studies in two related contexts that indicate disclaimers do not result in more informed decisions: disclaimers to health claims for dietary supplements as well as disclaimers in articles regarding industry funding.

Although disclaimers on dietary supplements may initially seem less analogous to off-label promotion of drugs to doctors since supplement disclaimers focus on consumers, supplement disclaimers importantly refer to the lack of FDA review regarding health benefits, which is analogous to off-label uses of drugs that have not been approved by the FDA.<sup>231</sup> In particular, dietary supplement companies can make claims lacking significant scientific agreement if they include a disclaimer that the health claim(s) are not reviewed by the FDA and that the supplement is not intended to treat any condition or disease.<sup>232</sup> However, a recent systematic review of seventeen published articles to empirically test a court suggestion that disclaimers could effectively warn doctors regarding unapproved uses of drugs concluded that consumers, including those that use supplements with disclaimers, are generally unaware of their existence, or that they did not attach any weight to the information in the disclaimer, as will be discussed.<sup>233</sup>

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230. Courts seem to intuit this in another context; in particular, in products liability cases involving failure to warn, courts have suggested that more warnings would not be better due to information overload. *Hood v. Ryobi Am. Corp.*, 181 F.3d 608, 611 (4th Cir. 1999) (noting that too many warnings make a label too long to read and too technical to understand); James A. Henderson, Jr. & Aaron D. Twerski, *Doctrinal Collapse in Products Liability: The Empty Shell of Failure to Warn*, 65 N.Y.U. L. REV. 265, 297–98 (1990) (noting that judges and juries erroneously assume warnings are costless in terms of harm). In addition, recent scholarship suggests that although many areas of the law suggest more information is better, consumers are not well poised to understand compelled disclosures. *E.g.*, Omri Ben-Shahar & Carl E. Schneider, *The Failure of Mandated Disclosure*, 159 U. PENN. L. REV. 647, 718 (2011); Kesten C. Green & J. Scott Armstrong, *Evidence on the Effects of Mandatory Disclaimers in Advertising*, 31 J. PUB. POL'Y & MARKETING 293, 302 (2012).

231. As a result of changes in the law that permit dietary supplements to be sold without the rigorous review of drugs, as well as First Amendment challenges, the FDA currently permits claims that lack significant scientific agreement to be made with certain disclaimers. *Guidance for Industry: Interim Procedures for Qualified Health Claims in the Labeling of Conventional Human Food and Human Dietary Supplements*, FOOD & DRUG ADMIN. (July 2003), <https://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/LabelingNutrition/ucm053832.htm> [<https://perma.cc/VTA4-HGAK>]. This is relatively recent, given changes in the regulatory framework in the mid-1990s, followed by First Amendment challenges. *See* Dietary Supplement Health and Education Act, Pub. L. No. 103-417, 108 Stat. 4325 (1994); *Whitaker*, 248 F. Supp. 2d at 2; *Pearson v. Shalala*, 164 F.3d 650, 655–60 (D.C. Cir. 1999).

232. 21 C.F.R. § 101.93(c) (2018) (“This statement has not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure, or prevent any disease.”).

233. *E.g.*, Kesselheim et al., *Mandatory Disclaimers*, *supra* note 96, at 444 (evaluating suggestion noted in *United States v. Caronia*, 703 F.3d 149, 179–80 (2d Cir. 2012)).

Multiple studies established that disclaimers on supplements had *no effect* on consumer belief regarding whether the product would have the claimed effect, or on the belief that the FDA had evaluated the claims.<sup>234</sup> The largest qualitative study to date involving 3500 adults indicated that about half of all surveyed adults believed that over-the-counter herbal products and weight-loss supplements are approved by a government agency, even though these products have disclaimers that clearly state they have not been reviewed by the FDA for effectiveness.<sup>235</sup> In addition, studies found that even for supplement-using consumers aware of disclaimers, some still believed that the FDA had tested the supplements or otherwise verified the accuracy of manufacturer claims.<sup>236</sup> Although supplement users may have cognitive biases that motivate them to believe in the safety of products they are using, the fact that even nonusers assume the FDA verifies claims suggests that such bias does not completely explain failure to understand FDA disclaimers.<sup>237</sup> Rather, it may be that in an

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234. E.g., Tonya Dodge & Annette Kaufman, *What Makes Consumers Think Dietary Supplements Are Safe and Effective? The Role of Disclaimers and FDA Approval*, 26 HEALTH PSYCHOL. 513, 516 (2007) (finding that FDA-required disclaimer resulted in only slight reduction in effectiveness belief with disclaimer, but no impact on beliefs about risks); Mary Meer, Scottie Misner & Ralph Meer, *Labeling of Dietary Supplements: Consumer Awareness and Industry Compliance*, 4 J. NUTRACEUTICALS FUNCTIONAL & MED. FOODS 29, 35 (2004) (finding that almost thirty percent of study participants were unaware of the existence of a disclaimer); Carla K. Miller & Teri Russell, *Knowledge of Dietary Supplement Label Information Among Female Supplement Users*, 52 PATIENT EDUC. & COUNSELING 291, 294–96 (2004) (in a study of dietary supplement users, two-thirds thought that the product had been approved by the FDA); Karen Russo France & Paula Fitzgerald Bone, *Policy Makers' Paradigms and Evidence from Consumer Interpretations of Dietary Supplement Labels*, 39 J. CONSUMER AFF. 27, 47 (2005) (finding that a disclaimer appeared to have no effect on belief that the product would have the claimed effect or that the FDA had reviewed the claimed effectiveness).

235. Janine L. Pillitteri, Saul Shiffman, Jeffrey M. Rohay, Andrea M. Harkins, Steven L. Burton & Thomas A. Wadden, *Use of Dietary Supplements for Weight Loss in the United States: Results of a National Survey*, 16 OBESITY 790, 791, 793 (2008) (finding that 48.8% of self-identified supplement users and 45% of nonusers agreed with statement that over-the-counter herbal products and weight-loss supplements must be approved for efficacy, or effectiveness by a government agency).

236. E.g., Marlys J. Mason & Debra L. Scammon, *Unintended Consequences of Health Supplement Information Regulations: The Importance of Recognizing Consumer Motivations*, 45 J. CONSUMER AFF. 201, 211 (2011); see also Miller & Russell, *supra* note 234, at 294 (noting that when presented with an actual disclaimer, more than thirty percent of participants failed to understand the FDA had not specifically approved or regulated the product).

237. In particular, supplement users are likely to have an over optimism bias that leads them to believe products they use are safer than they are. See Robert J. Blendon, Catherine M. DesRoches, John M. Benson, Mollyann Brodie & Drew E. Altman, *Americans' Views on Use and Regulation of Dietary Supplements*, 161 ARCHIVE INTERNAL MED. 805, 808 (2001). In addition, to the extent that they have a general belief that supplements are safe, that assumption will remain in the face of contrary evidence pursuant to confirmation bias, which seems to be reflected in studies. See *id.* at 807 (finding sixty-seven percent of supplement users indicated that if the FDA said a supplement was ineffective, that would not impact their decision to continue to take the supplement); Mason & Scammon, *supra* note 236, at 210, 214–15 (finding that supplement users who understood the FDA does not regulate supplements focused on

information-rich world already saturated with legal disclaimers, consumers are inured to them.<sup>238</sup> In addition, although disclaimers in real life could be overshadowed by other marketing messages, including more prominent images, such that there is incomplete processing,<sup>239</sup> even in controlled experimental settings without competing information or the presence of brand loyalty to a specific supplement, individuals still fail to understand the disclaimers.

Admittedly, the studies about disclaimers on supplements and lay consumers may not seem directly applicable to the allegedly more sophisticated doctors. However, studies consistently show that all individuals, including highly educated ones like doctors, are subject to the same cognitive biases. In addition, there are specific studies indicating physician behavior mirrors consumer behavior in marketing contexts, such that other researchers have suggested that supplement studies regarding consumers are analogous given the lack of any studies regarding physicians in particular.<sup>240</sup> In addition, there are studies on doctors in particular, and the impact of conflict of interest disclosures, as discussed below, that suggest there are serious limitations to the use of disclaimers to adequately inform doctors.

Accordingly, if companies present their alleged facts to doctors who are vulnerable to accepting such facts given the lack of competing information, any disclaimer to doctors about the lack of FDA review may similarly fall on deaf ears. This problem is compounded by the cognitive bias of anchoring in that the initial information from companies will be given more weight, or at least weight that is disproportional to the actual data. In addition, to the extent that companies tend to flood doctors with promotional materials, this information will seem more available and thus more relevant and accurate according to cognitive bias studies. However, all individuals, including experts, are subject to cognitive biases, and doctors are vulnerable to overconfidence bias that would likely make them even less likely to realize the impact of these heuristics. In addition, although the threat of a malpractice claim may theoretically seem a promising avenue to guard against bad decisions, that seems inconsistent with literature about the strength of cognitive biases. Moreover, malpractice claims are inherently tied to standard of care, and if there is no clear standard of care involving some off-label uses, malpractice threats would seem to be of little impact.

Just as disclaimers on nutritional supplements are intended to help provide information to ensure adequate discounting of possible bias, medical journals inform doctors about conflicts of interest to ensure that messages are appropriately discounted.<sup>241</sup> However, despite a more expert audience, there seem to be similar

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prior problems with FDA-regulated products and attributed disclaimers as some legal or bureaucratic necessity).

238. *E.g.*, Ben-Shahar & Schneider, *supra* note 230, at 689–90.

239. *See, e.g.*, Paul Biegler & Patrick Vargas, *Ban the Sunset? Nonpropositional Content and Regulation of Pharmaceutical Advertising*, 13 AM. J. BIOETHICS 3, 8 (2013) (noting consumers may be more influenced by positive associations suggested in advertisement than specific claims).

240. *E.g.*, Kesselheim et al., *Mandatory Disclaimers*, *supra* note 96, at 440.

241. *E.g.*, *Editorial Policies*, NEW ENG. J. MED., <https://www.nejm.org/about-nejm/editorial-policies> [<https://perma.cc/HRF3-JB7H>] (providing guidelines to ensure publication is free from commercial influence); *Instructions for Authors*, JAMA

problems processing these disclosures—even when they are actually made.<sup>242</sup> The disclosure statement may be entirely ignored,<sup>243</sup> or have the ironic effect of enhancing the trustworthiness of the discloser.<sup>244</sup> Although studies sometimes indicate doctors are more skeptical of industry-funded articles,<sup>245</sup> perhaps because

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<https://jamanetwork.com/journals/jama/pages/instructions-for-authors#SecDecisionsandManagementofEditorialConflictsOfInterest> [<https://perma.cc/MR2Z-5XHW>] (providing guidance on conflicts of interest); see also Phil B. Fontanarosa & Howard Bauchner, *Conflict of Interest and Medical Journals*, 317 J. AM. MED. ASS'N 1768, 1768–69 (2017) (explaining policy of all JAMA-related journals to mandate disclosure of conflicts regardless of amount of funding that will be disclosed in the acknowledgements section); INTERNATIONAL COMMITTEE OF MEDICAL JOURNAL EDITORS, *Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Works in Medical Journals*, INT'L COMM. MED. J. EDITORS, Dec. 2017, at 3–4, <http://www.icmje.org/icmje-recommendations.pdf> [<https://perma.cc/2VLA-9BWB>] (providing disclosure guidelines that many medical journals follow). Disclosure of conflicts is also an issue with continuing medical education. E.g., ACCREDITATION COUNCIL FOR CONTINUING MED. EDUC., STANDARDS FOR COMMERCIAL SUPPORT: STANDARDS TO ENSURE THE INDEPENDENCE OF CME ACTIVITIES 2 (2014) (stating that content not promoting a specific commercial interest and source of support from commercial interest must be disclosed to learners). However, there are some that believe merely identifying conflicts is not enough. E.g., AM. ACAD. FAMILY PHYSICIANS, CME POLICY AND PROCEDURES FOR FULL DISCLOSURE AND IDENTIFICATION AND RESOLUTION OF CONFLICTS OF INTEREST paras. 4(B), (D), <https://www.aafp.org/fpm/forms/coipolicy.pdf> [<https://perma.cc/3E8Q-8CE8>] (requiring that conflicts not merely be identified, but resolved, which could involve assigning a different topic for the individual, or else ensuring valid content through prior peer review or using evidence-based content); Bernard Lo & Chelsea Ott, *What is the Enemy in CME, Conflicts of Interest or Bias?*, 310 J. AM. MED. ASS'N 1019, 1019–20 (2013) (suggesting that identification of conflicts is only a rough proxy for commercial bias, and suggesting improvements to assess bias).

242. Sometimes articles are “written” by doctors paid by the industry, but this is not disclosed. See Aaron S. Kesselheim, Bo Wang, David M. Studdert & Jerry Avorn, *Conflict of Interest Reporting by Authors Involved in Promotion of Off-label Drug Use: An Analysis of Journal Disclosures*, PLOS MED., 2012, at 1, 7.

243. Silverman et al., *supra* note 209.

244. Steven D. Pearson, Ken Kleinman, Donna Rusinak & Wendy Levinson, *A Trial of Disclosing Physicians' Financial Incentives to Patients*, 166 ARCHIVES INTERNAL MED. 623, 625–26 (2006).

245. E.g., Aaron S. Kesselheim, Christopher T. Robertson, Jessica A. Myers, Susannah L. Rose, Victoria Gillet, Kathryn M. Ross, Robert J. Glynn, Steven Joffe & Jerry Avorn, *A Randomized Study of How Physicians Interpret Research Funding Disclosures*, 367 NEW ENG. J. MED. 1119, 1122 (2012) (doctors in experimental conditions were less likely to consider industry-funded trials as rigorous or inclined to prescribe drugs based on these studies compared to studies purportedly from the NIH based on the abstracts of hypothetical drugs); see also Samena Chaudhry, Sara Schroter, Richard Smith & Julie Morris, *Does Declaration of Competing Interests Affect Readers' Perceptions? A Randomised Trial*, 325 BRIT. MED. J. 1391, 1392 (2002) (subjects finding article that disclosed conflict of interest to be “significantly less interesting, important, relevant, valid, and believable” compared to article with no such disclosure); Sara Schroter, Julie Morris, Samena Chaudhry, Richard Smith & Helen Barratt, *Does the Type of Competing Interest Statement Affect Readers' Perceptions of the Credibility of Research? Randomised Trial*, 328 BRIT. MED. J. 743, 743 (2004) (finding that readers of British Medical Journal considered a study to be less important, relevant, valid,

they are aware that such articles disproportionately yield positive results,<sup>246</sup> other studies suggest that disclosure of industry funding or other conflict of interest do *not* impact how articles are perceived.<sup>247</sup> Most notably, one study showed that although doctors say they find industry-funded studies less persuasive, in an experimental setting regarding an abstract of a fictitious new drug, disclosure of funding from a company had no significant impact on self-reported prescribing likelihood.<sup>248</sup> Indeed, almost forty percent reported that they would not consider any type of conflict of interest by the author in deciding what to prescribe.<sup>249</sup> In other words, doctors seem to believe that they should discount for conflicts of interest, but have difficulty doing so; rather, doctors did not discount for bias at all. This is consistent with literature showing that people have difficulty ignoring information, such as a conflict of interest, in making decisions, even if they know that this information may bias their judgment.<sup>250</sup> In addition, this effect could also be a function of the fact that many doctors have relationships with pharmaceutical representatives and are motivated, albeit unconsciously, to ignore conflicts with pharmaceutical companies to preserve any potential cognitive dissonance.

There is additional data to debunk the more information schema in the context of conflict of interest disclosures in peer review articles that are presumed to lead to more reasoned judgments. Doctors generally only read abstracts,<sup>251</sup> which typically do not include conflict of interest disclosures since these usually appear at the end of

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or believable when associated with a financial interest disclosure). Of course, there are some that suggest financial interests alone do not necessarily indicate whether a study is reliable. E.g., David B. Resnik & Kevin C. Elliott, *Taking Financial Relationships into Account when Assessing Research*, 20 ACCOUNTABILITY IN RES.: POLICIES & QUALITY ASSURANCE 184, 194 (2013) (suggesting several factors be used to assess whether financial relationships impact research credibility).

246. See *supra* note 60 and accompanying text.

247. One study of actual abstracts from industry-funded trials indicated no statistically significant difference in interpretation of abstract findings regarding quality of methodology or treatment benefit. Buffel du Vaure et al., *supra* note 206, at 7–8.

248. See Silverman et al., *supra* note 209, at 267–68.

249. *Id.* at 267.

250. See, e.g., Lee Ross, Mark R. Lepper & Michael Hubbard, *Perseverance in Self-Perception and Social Perception: Biased Attributional Processes in the Debriefing Paradigm*, 32 J. PERSONALITY & SOC. PSYCHOL. 880 (1975); Timothy D. Wilson & Nancy Brekke, *Mental Contamination and Mental Correction: Unwanted Influences on Judgments and Evaluations*, 116 PSYCHOL. BULL. 117 (1994).

251. See Saint et al., *supra* note 206, at 883 (finding internists reported only reading abstracts for two-thirds of articles and suggesting that this may be an underestimation); see also Sally Hopewell, Anne Eisinga & Mike Clarke, *Better Reporting of Randomized Trials in Biomedical Journal and Conference Abstracts*, 34 J. INFO. SCI. 162, 162–63, 166 (2008) (noting that doctors may make treatment decisions based on reading abstracts); Robertson, *supra* note 60, at 368 (stating that physicians commonly choose to read only abstracts of articles through services such as PubMed). In addition, abstracts also may provide inaccurate conclusions. Roy M. Pitkin, Mary Ann Branagan & Leon F. Burmeister, *Accuracy of Data in Abstracts of Published Research Articles*, 281 J. AM. MED. ASS'N 1110, 1110–11 (1999) (noting that eighteen to sixty-eight percent of abstracts report findings inconsistent with or absent from the article's body, even in large-circulation medical journals).

an article. So, the inclusion of this additional information seems to realistically have no chance of actually informing doctors—even if the doctor was aware that industry-supported studies tend to be correlated with positive studies.<sup>252</sup> Moreover, even in the unlikely situation that a doctor reads the entire article, studies suggest that the abstract could have predominant influence pursuant to cognitive science studies regarding the effects of “anchoring”; in other words, initial information is given more weight, even if other information follows. This would also seem to be true in the unlikely event that a doctor skipped the abstract and read the article; since the conflict of interest disclosures do not come until the end, the doctor’s opinion is likely already anchored to the information disclosed before such disclosures. Moreover, even if doctors actually read the conflict of interest disclosure and were appropriately skeptical of industry-funded articles, that might be of no utility if industry-funded articles are the only source of information.

### III. IMPLICATIONS

This Part evaluates how commercial speech law currently overprotects marketing of off-label uses of drugs. Section A explains why the previously unrecognized schemas discussed above have contributed to an expansion of commercial speech rights in this area. Then, Section B examines whether there are better First Amendment policies to emphasize with such promotion.

#### *A. Retrospective View on First Amendment Expansion Informed by Cognitive Bias*

This Section takes a fresh look at recent commercial speech cases regarding off-label marketing of prescription drugs. This Section first reviews key facts from recent cases. Then, it examines how schemas have impacted evaluation of facts, as well as application of the law. Finally, this Section explains how FDA capitulation to judicial challenges has resulted in the fact that schemas are currently baked into precedent.

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252. There is consistent evidence that studies financially supported by self-interested industries are more likely to provide outcomes favorable to those industries. *E.g.*, Justin E. Bekelman, Yan Li & Cary P. Gross, *Scope and Impact of Financial Conflicts of Interest in Biomedical Research: A Systematic Review*, 289 J. AM. MED. ASS’N 454, 456 (2003); Joel Lexchin, Lisa A. Bero, Benjamin Djulbegovic & Otavio Clark, *Pharmaceutical Industry Sponsorship and Research Outcome and Quality: Systematic Review*, 326 BRIT. MED. J. 1167, 1168–69 (2003); Andreas Lundh, Joel Lexchin, Barbara Mintzes, Jeppe B. Schroll & Lisa Bero, *Industry Sponsorship and Research Outcome*, COCHRANE LIBR., 2013, at 12; Sergio Sismondo, *Pharmaceutical Company Funding and Its Consequences: A Qualitative Systematic Review*, 29 CONTEMP. CLINICAL TRIALS 109 (2008); *see also* Bodil Als-Nielsen, Wendong Chen, Christian Gluud & Lise L. Kjaergard, *Association of Funding and Conclusions in Randomized Drug Trials: A Reflection of Treatment Effect or Adverse Events?*, 290 J. AM. MED. ASS’N 921, 925 (2003) (noting that studies supported by for-profit organizations are more likely to recommend experimental drug for treatment).

### 1. Relevant Case Law Expanding Commercial Speech for Off-Label Promotion

Before analyzing the impact of schemas on how courts evaluate facts and conduct legal analysis, a brief review of the core facts of cases is essential. As discussed earlier, the first commercial speech case involving off-label promotion was the 1998 *Washington Legal Foundation* decision.<sup>253</sup> In that case, two FDA guidance documents that barred pharmaceutical companies from showing doctors scientific articles relating to drugs were deemed unconstitutional for restricting free speech.<sup>254</sup> The FDA did not challenge this district court decision.<sup>255</sup> Accordingly, the next important commercial speech case involving pharmaceutical companies is the 2011 Supreme Court *Sorrell* decision.<sup>256</sup>

In 2011, the Supreme Court issued the *Sorrell* decision, which is related to off-label promotion of drugs but does not squarely address the extent to which the FDA can regulate such promotion consistent with commercial speech.<sup>257</sup> *Sorrell* involved a challenge by drug companies to a Vermont law barring companies from buying data concerning doctor prescriptions to use it to more effectively sell drugs to doctors (i.e., for detailing by representatives).<sup>258</sup> A 6-3 majority found that the Vermont law unduly hindered commercial speech and even suggested that commercial speech might be subject to heightened judicial scrutiny if it is content or speaker based.<sup>259</sup> Although the majority found that Vermont's law targeted only pharmaceutical companies, and thus was arguably speaker based, it did not ultimately propose any new standard and instead found the Vermont law failed under the traditional *Central Hudson* test.<sup>260</sup>

The first true First Amendment challenge to off-label marketing was in *United States v. Caronia*, which involved a criminal prosecution for misbranding.<sup>261</sup> The case involved an unusual situation where the pharmaceutical sales representative was not only caught on tape promoting the drug for an unapproved uses, but also for situations subject to a black box warning.<sup>262</sup> In other words, the sales representative was actually providing untruthful information. The FDA, however, made the strategic decision not to challenge the falsity of the information. The Second Circuit majority opinion in *Caronia* reversed the conviction against the sales representative,

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253. Wash. Legal Found. v. Friedman, 13 F. Supp. 2d 51 (D.D.C. 1998).

254. *Id.* at 54, 73–74.

255. The FDA and Washington Legal Foundation (WLF) reached an agreement that guidance documents were merely “safe harbors” from prosecution that mooted the need for an appeal of this decision as well as a related challenge to a new law permitting manufacturer dissemination of off-label use if the manufacturer had applied or intended to apply for a new use. Krause, *supra* note 83, at 409.

256. *Sorrell v. IMS Health Inc.*, 564 U.S. 552 (2011).

257. *See id.*

258. *Id.* at 558–61.

259. *Id.* at 580.

260. *Id.* at 572.

261. 703 F.3d 149 (2d Cir. 2012).

262. *Id.* at 155–57 (although the black box warning stated that drug safety and efficacy had not been established for those under sixteen and that the drug had “very limited” experience among elderly patients, the sales representative was recorded saying that the drug was “a very safe drug” to patients, including those as young as fourteen and greater than sixty-five).



finding that the FDA improperly relied on off-label promotion *alone* as the basis of the misbranding claim, rather than as evidence of intent to misbrand.<sup>263</sup>

Subsequently, pharmaceutical manufacturer Amarin, together with four doctors, sought a preliminary injunction against the FDA in the Southern District of New York, where *Caronia* was precedential.<sup>264</sup> In particular, Amarin wanted the court to enjoin the FDA from bringing a misbranding action<sup>265</sup> for an unapproved use of a drug after the FDA denied approval for that use as not scientifically justified.<sup>266</sup> Although only the FDA can approve a new use, Amarin's legal challenge was effectively an attempt to overrule the FDA decision denying approval. Amarin, however, characterized its effort as simply an attempt to shield itself from prosecution for making truthful statements in a format different than the FDA prefers.<sup>267</sup>

## 2. Examining Key Cases Through the Lens of the Revealed Schemas

Examining recent commercial speech cases concerning off-label promotion through the lens of the two schemas provides new insight to complement existing criticism of these cases. As will be discussed, these schemas impact how courts evaluate facts, as well as the application of relevant law.

Schemas serve as an important framework through which facts are evaluated. This is well illustrated in the *Sorrell* majority opinion which found a Vermont law barring pharmaceutical companies from obtaining and using doctor prescriptions to inform their detailing to violate protections on commercial speech.<sup>268</sup> The majority stated that there were "divergent views" regarding the value of detailing, as well as the value of prescribing brand name drugs, but nonetheless seemed more inclined to assume the information valuable and consistent with the more information schema.<sup>269</sup> This schema likely led the majority to fail to recognize the inherently unbalanced prescription marketplace where companies have outsized resources and incentives to promote a view that cannot be matched by a state.<sup>270</sup> The dissent, on the other hand,

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263. *Id.* at 168–69.

264. *Amarin Pharma, Inc. v. FDA*, 119 F. Supp. 3d 196 (S.D.N.Y. 2015); *see also* Krause, *supra* note 83, at 414–15 (noting that the case was intentionally filed in a district where *Caronia* would be precedential).

265. *See Amarin*, 119 F. Supp. 3d at 221.

266. *Id.* at 209 (noting desire to promote unapproved drug use for patients with merely "persistently" high triglyceride levels in addition to the approved use for patients with *very high* levels).

267. *Id.* at 223. This case was different than the prior cases not only because of its procedural posture, but also because the drug at issue, marketed as Vascepa, is actually a purified version of fish oil, and supplements made of unpurified fish oil may be marketed without the rigorous review required of drugs, so long as a company provides a disclaimer to note the lack of a review. *See id.* at 237. In addition, although the FDA had a legal basis to deny approval of the proposed new use, Amarin had entered into a special agreement with the FDA before doing the clinical trial for the proposed new use that typically leads to approval. *Id.* at 210.

268. *Sorrell v. IMS Health Inc.*, 564 U.S. 552 (2011).

269. *Id.* at 578.

270. *See id.*

recognized that the majority's suggestion that the state could promote contrary speech was not realistic, citing information in the record to counter the majority's presumptions.<sup>271</sup> The more information schema may also underlie the majority's emphasis on the possible value of new drugs that are subject to detailing—when the issue was not about promoting all new drugs. Rather, as recognized by the dissent, the challenge was only regarding whether companies could more successfully market new drugs not based on a superior product, but on knowledge of doctor preferences.<sup>272</sup>

The schemas also play an important role in how courts evaluate regulations that impact commercial speech. The traditional benchmark for evaluating such speech is the intermediate scrutiny test announced in *Central Hudson*. Although the *Sorrell* majority suggested heightened scrutiny should apply to any regulation that it is not content neutral (i.e., allegedly targeting only pharmaceutical companies)<sup>273</sup> it did not articulate, let alone apply, such a test nor have any subsequent cases, as noted earlier. Accordingly, how schemas impact judicial evaluation of the *Central Hudson* factors remains an issue. Examples of the impact of schemas on judicial interpretation of the factors in key cases relating to promotion of off-label use of drugs are discussed below within the framework of the *Central Hudson* factors.

#### i. False or Inherently Misleading?

The schemas have played a role in judicial analysis of the first *Central Hudson* factor (i.e., whether the commercial speech is aimed at a lawful purpose and whether the speech is false or inherently misleading).

The first case to embrace First Amendment challenges to off-label use restrictions, *Washington Legal Foundation*, seemed influenced by these schemas in rejecting the FDA suggestion that publications from companies were false or inherently misleading. The court acknowledged that the FDA had provided the court with “substantial evidence” that research from companies impacted actual prescriptions

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271. *Id.* at 593–95. As recognized by the dissent, attempts to mirror the methods of the prescription drug industry with “academic” or “counter” detailing (i.e., a presentation by an individual to a doctor on the benefits of generic drugs or alternative treatments) have not been found adequate to counter the imbalanced sales tactics at issue here. *Id.* at 601 (Breyer, J., dissenting).

272. *See id.* at 595, 596 (Breyer, J., dissenting) (noting that because, as the majority stated, state law intended to impose a “specific, content-based burden,” heightened judicial scrutiny is warranted in evaluating government regulation of speech because of disagreement with the message). Arguably, this suggestion could be a result of the convergence of the sophisticated doctor and more information schemas. Of course, this is not to suggest that these schemas are the only possible explanation. Alternatively, the majority could be reflecting a return to the *Lochner* era where courts substituted their own judgment in evaluating regulations. *See id.* at 591–93 (Breyer, J., dissenting) (cautioning that second-guessing legislative decisions would be a dangerous return to the “happily bygone era” in *Lochner* when judges abused their power to impose their own economic theories). Nonetheless, recognizing the effect of combining both schemas in this case may help explain the majority's suggestion for this new standard.

273. *Id.* at 565.

and sales,<sup>274</sup> and even acknowledged that manufacturers would only “disseminate information that presents their product in a favorable light,” with the potential to mislead in the context of concluding that the information was commercial speech.<sup>275</sup> However, the court did not mention these issues in analyzing whether the information was in fact inherently misleading, even though it acknowledged that determining whether something is inherently misleading depends upon possibilities for deception, which its earlier discussion seemed to suggest is possible.<sup>276</sup> Even though the court realized that companies would likely selectively provide certain data to companies, the court asserted that publications could not be inherently deceptive when provided by one self-interested company versus another.<sup>277</sup> Although the court did not explicitly say so, it may have been relying on the sophisticated doctor schema to assume that doctors would know publications from companies were not reliable and thus perhaps merely “potentially,” rather than inherently, misleading.<sup>278</sup>

This lack of concern for deception may be tied to another issue the court notes as important in evaluating what is inherently misleading—the ability of the audience to evaluate the claims made.<sup>279</sup> Although doctors cannot actually evaluate any of the scientific claims on their own without conducting their own research, which is highly unlikely, the court’s lack of concern that doctors will be misled seems to be tied to the sophisticated doctor schema. For example, in noting that a prior court had denied a constitutional challenge to FDA regulations requiring health claims to be supported by significant scientific agreement, the court asserted that the case at issue concerned a “professional audience,” without discussion of whether that audience could actually evaluate the scientific claims.<sup>280</sup> In addition, the more information schema may have influenced the court to conclude that publications from a manufacturer were not inherently misleading because the FDA could indicate that uses had not been approved and require publications only from “bona fide peer-review” journals and independent publishers, presumably based on the assumption that such sources are scientifically reliable.<sup>281</sup>

The more information schema may have played a particularly powerful role in the *Caronia* decision that overruled a criminal conviction against a sales representative for misbranding, based in part from promoting an off-label use that could have led to serious public health harm and was subject to a black box warning.<sup>282</sup> This schema may explain something that has perplexed scholars—the fact that the majority repeatedly emphasized that the information was “truthful,” when in fact it was

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274. *Wash. Legal Found. v. Friedman*, 13 F. Supp. 2d 51, 63 (D.D.C. 1998).

275. *Id.* at 65.

276. *See id.* at 66–69.

277. *See id.*

278. The court stated “the exact same journal article or textbook reprint cannot be inherently conducive to deception and coercion when it is sent unsolicited” by a manufacturer. *Id.* at 67. However, this seems contrary to the court’s prior acknowledgement that manufacturers will, in fact, selectively send only information favorable to their product.

279. *See id.* at 67.

280. *Id.* at 68.

281. *Id.*

282. *United States v. Caronia*, 703 F.3d 149, 155–56 (2d Cir. 2012).

patently false.<sup>283</sup> Of course, it is true that the FDA never alleged that the information was false, such that the court was legally permitted to infer the information was truthful.<sup>284</sup> In addition, in the preliminary discussion of facts, the majority did note that the sales representative promoted uses with populations that the FDA not only had not approved, but for which there was a “black box” warning; such a warning is the most serious warning possible for prescription labels.<sup>285</sup> However, the more information schema could help explain why the court did not explicitly state in the text to its *Central Hudson* analysis that it was *presuming* the information was not false or misleading because it was uncontested even though the discussion of facts acknowledged the information was not only false, but dangerous.<sup>286</sup> In other words, this case demonstrates how the more information schema not only results in treating potentially misleading information equivalent to truthful information, but that it may also result in a court presuming information is truthful contrary to actual facts. Even though the court was permitted as a matter of law to presume the information was true, the more information schema provides an important explanation for why the court seemed to discount the facts in its own opinion that contradict this assumption.

#### ii. Substantial Government Interest?

The same schemas may have contributed to the court’s decision in *Washington Legal Foundation* that no substantial government interest in ensuring doctors have accurate and unbiased information. In particular, although the court recognized that there was a substantial government interest in encouraging companies to submit new drug uses to the FDA for approval,<sup>287</sup> the court completely rejected the FDA’s suggestion that there was a substantial government interest in ensuring doctors had accurate and unbiased information.<sup>288</sup> This rejection seems grounded in the more information schema that assumes even potentially misleading information can be “informative,” as well as the sophisticated doctor schema that erroneously assumes doctors will not be misled by marketing information.

Similarly, the schemas may have contributed to the *Sorrell* majority narrowly defining the relevant government interest behind the state law intended to bar drug

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283. Krause, *supra* note 83, at 432 (noting that the court’s conclusion was “curious” since Caronia’s statement directly contradicted the black box warning); *see also Caronia*, 703 F.3d at 166, 168.

284. This likely reflected the litigation strategy since a holding that does not rely on false statements would be broader. *See Greene*, *supra* note 5, at 683 (noting that the government believed it only needed to show that the drug was promoted for off-label use).

285. *Caronia*, 703 F.3d at 155–56; *see also supra* note 262 and accompanying text (providing details of the black box warning); *supra* note 188 and accompanying text (explaining black box warnings).

286. *See id.* Of course, the existence of an information schema does not mean that there are not additional issues contributing to the decision, such as that the court might have been concerned about criminal liability for a sales person for misbranding, as opposed to a corporation or a high-level executive. *E.g., id.* at 174 (Livingston, J., dissenting). Nonetheless, the information schema can add insight.

287. *Wash. Legal Found. v. Friedman*, 13 F. Supp. 2d 51, 71–72 (D.D.C. 1998).

288. *Id.* at 69–70.

companies from using doctor prescription records. In particular, in discussing the government interest, the majority characterized the main interest as medical privacy, as well as preventing harassing behavior by sales representatives.<sup>289</sup> In addition, the majority relied on the sophisticated doctor schema to dismiss the suggestion that the state law did not directly advance the goal of minimizing harassing behavior because doctors can and do deny meetings with detailers.<sup>290</sup> The majority also embraced the more information schema in arguing that detailers had valuable information for doctors—even though the information sought was only valuable to the detailers to promote sales, and not doctors.<sup>291</sup> The majority discounted a state interest in limiting the success of pharmaceutical detailing to help reduce drug costs because the state did not vigorously pursue this during oral argument.<sup>292</sup> However, there was a substantial legislative record behind the policy goal of reducing detailing success to reduce costs, as duly noted by the dissent.<sup>293</sup> The majority seemed to thoroughly embrace the more information schema in characterizing detailing as “benign and, many would say, beneficial speech,” and also by asserting that the possibility that detailing might persuade “provides no lawful basis for quieting it.”<sup>294</sup>

### iii. Direct Advancement of Interest?

Although the *Sorrell* majority narrowly defined the government interest, and thus easily rebutted why these interests were not advanced, it still considered whether the government interest of reducing brand name drug costs was directly advanced—all while being influenced by the schemas. However, as the dissent pointed out, the challenged state law did directly advance a government interest by ensuring discussion is based on actual facts about drugs, rather than using past doctor prescriptions to sway doctors.<sup>295</sup>

The *Sorrell* majority repeatedly relied on schemas to support its assertion that the regulation did not directly advance any government interest. For example, the majority noted that doctors find detailing “instructive”—consistent with the sophisticated doctor schema, as well as the more information schema.<sup>296</sup> The court also noted that the common First Amendment refrain that truthful information should not be suppressed based on the fear of bad decisions (i.e., the more information schema) applies with “full force” when the audience consists of “*sophisticated and experienced consumers*.”<sup>297</sup> In doing so, the majority quoted *Edenfield*, a case that found a law banning certified public accountants (CPAs) from personal solicitation to be unconstitutional since prospective clients were likely sophisticated and

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289. *Sorrell v. IMS Health Inc.*, 564 U.S. 552, 572–74 (2011).

290. *Id.* at 575.

291. *Id.* at 575–77.

292. *Id.* at 576–78.

293. *Id.* at 597–98 (Breyer, J., dissenting) (finding a broader substantial interest to regulate public health consistent with police powers).

294. *Id.* at 576 (citing *Brandenburg v. Ohio*, 395 U.S. 444, 447 (1969)) (noting that fear of persuasion is not a lawful basis for quieting speech in most situations, including this case).

295. *Id.* at 597 (Breyer, J., dissenting).

296. *Id.* at 578.

297. *Id.* at 577 (emphasis added) (quoting *Edenfield v. Fane*, 507 U.S. 761, 775 (1993)).

experienced business executives not prone to manipulation.<sup>298</sup> However, that case found no dangers for professionals subject to in-person solicitation by a CPA *who is not trained in the “art of persuasion.”*<sup>299</sup> Although doctors are professionals, they are being approached by pharmaceutical representatives whose livelihood fundamentally depends on being persuasive.<sup>300</sup> In fact, companies are known to hire those they consider most likely to be persuasive.<sup>301</sup>

The schemas may help explain some of the discussion in the *Caronia* majority opinion concerning the direct advancement of interest. Although the majority recognized that the government has a substantial interest in preserving the integrity of the drug approval process and reducing patient harm from unsafe and ineffective drugs, its reliance on the information schema seemed to unduly contribute to its conclusion that a bar on off-label marketing of “truthful” information fails to directly advance this interest.<sup>302</sup> In particular, the majority’s assertion that FDA regulations legalize off-label use, but “prohibit[] the free flow of information that would inform that outcome,”<sup>303</sup> reflects the more information schema in conjunction with the sophisticated doctor schema that falsely presumes doctors are not misled by marketing. So, the majority’s assertion that drug companies were providing “potentially relevant treatment information” that will provide “informed and intelligent treatment decisions” does not comport with reality.<sup>304</sup> There are also systematic problems with relying on the schemas. As recognized by the dissent, permitting a company to promote a drug for any use after the drug has been only approved for *one* would fundamentally disrupt the entire process for drug approval and portends that the entire process could be found unconstitutional.<sup>305</sup>

#### iv. Narrowly Tailored

In addition, the *Caronia* majority’s suggestion that prosecution of off-label marketing is not narrowly tailored is also questionable once cognitive biases are taken into consideration.<sup>306</sup> For example, the majority suggested that a less speech-

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298. *Id.* In addition, in *Edenfield*, the Court noted that CPA training emphasizes independence and objectivity, not advocacy, which are likely inapplicable to drug representatives. *See Edenfield*, 507 U.S. at 775.

299. *Id.* (emphasis added).

300. Not only are pharmaceutical representatives hired to be persuasive, but about a quarter of their overall compensation is tied to prescriptions written by physicians. *See Christopher v. SmithKlein Beecham Corp.*, No. CV-08-1498-PHX-FJM, 2009 WL 4051075, at \*3 (D. Ariz. Nov. 20, 2009).

301. *E.g.*, Stephanie Saul, *Gimme an Rx! Cheerleaders Pep Up Drug Sales*, N.Y. TIMES (Nov. 28, 2005), <https://www.nytimes.com/2005/11/28/business/gimme-an-rx-cheerleaders-pep-up-drug-sales.html> [<https://perma.cc/49YU-88VG>].

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

303. *Id.* at 167.

304. *Id.* at 166.

305. *See id.* at 179.

306. In contrast, the *Caronia* dissent seemed to implicitly understand that more information is not always better in considering misbranding to be the least restrictive way to advance the government interest in protecting the new drug approval process, which the Supreme Court has previously recognized as an important government interest. *Id.* at 178.

restrictive alternative could be to educate doctors regarding potentially misleading information.<sup>307</sup> However, this suggestion is questionable based on what studies have shown: doctors are already skeptical of the accuracy of information from pharmaceutical companies, and yet are still vulnerable to the marketing messages far more than they realize.<sup>308</sup> In addition, as discussed earlier, it is difficult to change preexisting schemas due to confirmation bias that impacts all individuals.<sup>309</sup> That is, if a doctor believes that she is capable of distinguishing misleading information from true information—even if she is in fact incapable of doing so—she is likely to ignore subsequent information inconsistent with her beliefs. So, simply telling doctors that they are vulnerable to being misled is not likely to be adequate alone.

The information schema also seemed highly relevant to the *Amarin* decision that followed *Caronia*. The court noted that it wanted to “err on the side of caution,” which meant providing doctors with more, not less, information, consistent with the more information schema.<sup>310</sup> Since the plaintiff-doctors alleged the information was helpful, the court did not question this belief, even though, as previously discussed, studies show doctors are in fact far less sophisticated than they realize.<sup>311</sup>

The more information schema is reflected in the *Amarin* court’s evaluation and approval of a proposed statement regarding how certain omega-3 fatty acids, present in *Amarin*’s drug marketed as Vascepa, may reduce heart disease according to “[s]upportive but not conclusive research.”<sup>312</sup> Although the FDA considered this to be potentially misleading, the court focused on the fact that the FDA did not challenge the claim as *completely* misleading.<sup>313</sup> In other words, the court’s lack of concern regarding potentially misleading information is consistent with the more information schema that does not question harm from potentially misleading information.<sup>314</sup> The court noted that the accompanying disclosures would easily address any such problem.<sup>315</sup> However, as explained in Section II.C, relying on disclosures to actually inform is not supported by empirical studies.

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307. *Id.* at 168.

308. *See supra* Section II.B.2.

309. *See supra* Section II.A.2.

310. *Amarin Pharma, Inc. v. FDA*, 119 F. Supp. 3d 196, 233 (S.D.N.Y. 2015).

311. *See supra* Section II.B.

312. *Amarin*, 119 F. Supp. 3d at 214. *Amarin* proposed the following Statement (#1): “Supportive but not conclusive research shows that consumption of EPA and DHA omega-3 fatty acids may reduce the risk of coronary heart disease.” *Id.* at 234. Similarly, the information schema likely led the court to permit *Amarin* to add additional language to the FDA’s proposed statement regarding the fact that recent trials failed to demonstrate the cardiovascular benefit of adding a second lipid-altering drug when it characterized the industry desired language as “factually accurate,” and relegated to a footnote its dismissal of the FDA’s assertion that the language was misleading. *Id.* at 233 n.65.

313. *Id.* at 235.

314. *See id.* at 234.

315. *Id.* at 235 (noting FDA concern that a doctor might improperly conclude that “there is currently sufficient evidence to support a conclusion that drug-induced decreases in triglyceride levels lead to a reduction in the risk of cardiovascular events in patients on statin therapy.”). The other agreed upon disclosures are that the “FDA has not approved Vascepa to reduce the risk of coronary heart disease” (*Amarin* Disclosure #1); “[t]he effect of Vascepa on the risk of cardiovascular mortality and morbidity has not been determined” (*Amarin*

### 3. Schemas Baked into Precedent Result in FDA Capitulation

The two schemas are currently entrenched in commercial speech precedent in part as a result of a lack of government challenges to prior rulings. Although the lack of government challenges to prior rulings can be considered reasonable to avoid potential court decisions that could threaten the entire FDA new drug-approval process, government inaction could ironically lead to the same conclusion. To best understand the current situation, it is important to begin with the first case to use the First Amendment to challenge FDA regulation of off-label uses (i.e., *Washington Legal Foundation*) since the FDA's response to that has impacted subsequent cases.

*Washington Legal Foundation* was a key case in finding FDA regulations barring companies from distributing peer-reviewed articles concerning off-label uses to violate commercial speech. After losing the summary judgment motion in *Washington Legal Foundation*, the FDA effectively conceded companies could distribute peer-reviewed articles that support off-label uses.<sup>316</sup> However, empirical studies conducted since the case was decided in 1998 now show serious problems with peer-reviewed articles, even if they have the veneer of objectivity.<sup>317</sup> But, because the FDA settled, subsequent courts have used this decision to suggest that the FDA itself acknowledges that such articles are helpful.<sup>318</sup>

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Disclosure #3); “[a] cardiovascular outcomes study of Vascepa designed to evaluate the efficacy of Vascepa in reducing cardiovascular mortality and morbidity in a high risk patient population on statin therapy is currently underway” (Amarin Disclosure #4); and “Vascepa may not be eligible for reimbursement under government healthcare programs . . . to reduce the risk of coronary heart disease . . .” (Amarin Disclosure #5); as well as contested Amarin Disclosure #2, which stated that the “FDA has not approved Vascepa for the treatment of statin-treated patients with mixed dyslipidemia and high . . . triglyceride levels.”

316. See U.S. FOOD & DRUG ADMIN., GOOD REPRINT PRACTICES FOR THE DISTRIBUTION OF MEDICAL JOURNAL ARTICLES AND MEDICAL OR SCIENTIFIC REFERENCE PUBLICATIONS ON UNAPPROVED NEW USES OF APPROVED DRUGS AND APPROVED OR CLEARED MEDICAL DEVICES (2009), <https://www.fda.gov/regulatoryinformation/guidances/ucm125126.htm> [<https://perma.cc/K5QV-4SG5>]. The details that led to this are a bit complex. Basically, before the district court ruling in favor of the Washington Legal Foundation (WLF), Congress passed the Food and Drug Administration Modernization Act of 1997 (FDAMA), which permitted information about unapproved uses so long as the manufacturer had applied or intended to apply for a new use. Pub. L. No. 105-115, 111 Stat. 2296 (codified as amended at 21 U.S.C. § 360). Although the FDA initially thought the WLF ruling enjoining its previously challenged guidance documents did not apply to the new statute, after the district court enjoined enforcement of FDAMA and its implementing regulations, the government initially appealed, but reached an agreement with WLF that it had no independent prosecutorial authority, only the ability to provide a “safe harbor” from prosecution. *Wash. Legal Found. v. Henney*, 202 F.3d 331, 335–36 (D.C. Cir. 2000); see also Krause, *supra* note 83. In addition, although FDAMA provisions were written to sunset in 2006, the 2009 FDA guidance document was more beneficial to companies because they could provide documents concerning off-label uses without any need to have an intent to submit an application to the FDA for approval of that use. Krause, *supra* note 83, at 410.

317. See *supra* notes 59–60 and accompanying text.

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



More recently, the *Amarin* court recognized that there was a “vigorous dissent” in *Caronia* but also noted that the FDA failed to challenge this decision, seeming to suggest that this means that the *Caronia* majority was necessarily correct.<sup>319</sup> Although many commentators recognize that the FDA’s failure to challenge judgments and enter into settlements is inherently tied to concern about further erosion of its regulatory powers, its inaction has opened the door to courts questioning its basic regulatory authority. For example, the *Amarin* court asserted that the FDA process for approving even new drugs “predates modern [sic] First Amendment law respecting commercial speech.”<sup>320</sup> The FDA did not challenge this, likely because an appeal would have been futile since the case was filed in the Southern District of New York and governed by *Caronia*.<sup>321</sup> Nonetheless, the *Amarin* suggestion is a troubling one that subsequent courts can now rely on. In addition, this troubling suggestion may result in further FDA capitulation to settlements in other cases.

### *B. The Mismatch Between First Amendment Policy and Pharmaceutical Marketing*

There is currently a stark mismatch between First Amendment policy and marketing of prescription drugs. Although commercial speech cases consistently assert that well-informed decisions are a goal, this is often an elusive one, with dangerous public health consequences looming in the context of promoting unapproved uses of prescription drugs. As previously discussed, it is difficult for doctors to make informed prescription decisions when they rely on information from self-interested companies. This Section explains that although case law recognizes misleading commercial speech as raising policy concerns that justify more regulation, cases thus far fail to see that many of these concerns exist in the context of potentially misleading speech from pharmaceutical companies that speak in a one-sided marketplace. This Section explains why recognition of these similarities is important to achieve the policy goal of informed decisions.

#### 1. Policy Similarities Between Inherently and Potentially Misleading Speech

Although it is undisputed that inherently misleading commercial speech may be barred, the policy concerns behind such speech are actually similar to those of potentially misleading speech. For example, the *Amarin* court stated that “[w]hether speech is ‘inherently misleading’ depends on . . . the ‘possibilities for deception,’ . . . whether ‘experience has proved that in fact that such advertising is subject to abuse,’ . . . and ‘the ability of the intended audience to evaluate the claims made.’”<sup>322</sup>

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319. *Amarin*, 119 F. Supp. 3d at 227.

320. *Id.* at 226.

321. The FDA promptly settled after the court’s holding in favor of granting a preliminary injunction against the FDA, essentially permitting the company to assert their desired claims. See Eric Palmer, *With FDA Settlement, Tiny Amarin Creates Opening for Pharma in Off-Label Marketing*, FIERCEPHARMA (Mar. 9, 2016, 10:10 AM), <https://www.fiercepharma.com/pharma/fda-settlement-tiny-amarin-creates-opening-for-pharma-off-label-marketing> [https://perma.cc/KS9X-72AY].

322. *Amarin*, 119 F. Supp. 3d at 235 (quoting *Wash. Legal Found. v. Friedman*, 13 F. Supp.

Although not recognized by courts thus far due to the two schemas, doctors, who are the intended audience of pharmaceutical marketing, have no ability to verify accuracy of pharmaceutical marketing since there is no other source of information. In addition, although not yet recognized by courts, studies show that doctors are vulnerable to advertising, yet are largely unaware of their vulnerability.

Detailing has characteristics similar to those previously noted as problematic in commercial speech cases regarding misleading information that can be banned. In particular, the Supreme Court has previously given states more liberty to restrict speech in situations where there is a danger of overreaching. This can happen when someone who is “trained in the art of persuasion” is in a situation that would breed “undue influence,” such as an attorney who is soliciting at an accident site or hospital room.<sup>323</sup> As noted earlier, sales representatives are hired to be persuasive, and their livelihood depends on it.<sup>324</sup> Studies show that these representatives have undue influence on doctors based not on a superior product, but on their effective use of marketing techniques known to take advantage of psychological biases. Indeed, the fact that many doctors claim the information from representatives is useful without impacting them—contrary to actual studies from evidence—shows that they are subject to influence. Whereas there is general consumer skepticism concerning attorneys that might make even an accident victim leery of such a solicitation, doctors’ assertions of the value of pharmaceutical detailing underscore that representatives are so persuasive that doctors are largely unaware that they are being manipulated.

Also, the Supreme Court has noted that deception is more likely when there is a limited ability to self-police and a lack of standardization in the product.<sup>325</sup> Although these comments were made about attorney advertisements (where the product is attorney advice, which is usually individualized), the absence of self-policing and a standard product apply equally to the field of pharmaceutical marketing.<sup>326</sup> It is clear that the industry is not self-policing its own conduct considering a long history of companies being fined for improperly advertising off-label use of drugs.<sup>327</sup> In addition, there is no standardization for off-label drug marketing; the FDA only regulates the uses that it has evaluated, not off-label uses.<sup>328</sup> Of course, the case that

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2d 51, 67 (D.D.C. 1998) (internal citations omitted).

323. *Ohralik v. Ohio State Bar Ass’n*, 436 U.S. 447, 461, 464–65 (1978).

324. *See supra* notes 300–301 and accompanying text.

325. *See In re R.M.J.*, 455 U.S. 191, 202 (1982) (relying extensively on *Bates v. State Bar of Ariz.*, 433 U.S. 350 (1977), to establish that there is no absolute bar on potentially misleading information and that the attorney advertising in case at issue was not actually misleading to include information about where the attorney was licensed to practice or to mail cards announcing the opening of an office).

326. In addition, they are arguably even more concerning in the context of off-label marketing since there are public health harms from misleading drug advertisements but generally not regarding attorney advertisements.

327. *See, e.g., supra* notes 84–86 and accompanying text; *see also Amarin*, 119 F. Supp. 3d at 204 (“There are many examples in which prescriptions of an approved drug for off-label use has caused harm.”).

328. *See* 21 C.F.R. § 201.57(a)(3) (2015) (requiring labeling only for approved uses of drugs). The FDA regulates labeling of approved uses of drugs, but does not directly regulate unapproved uses. *Id.*; *see also supra* Section I.A (explaining that the FDA approves drugs for

mentioned these issues also noted the public's comparative lack of knowledge as a key factor, which would seem initially inapplicable to doctors.<sup>329</sup> However, as explained in Part II, although doctors are highly educated, they are far less sophisticated than the sophisticated doctor schema assumes, and studies show that they actually have been misled. So, rather than deception being simply a theoretical issue that courts readily dismiss as improbable, it is in fact often the reality.

## 2. Potentially Misleading Pharmaceutical Marketing Is Unlikely to Be Corrected, with Significant Public Harm, but Limited Benefit

An important issue with marketing of prescription drugs is that the traditional presumptions concerning how potentially misleading speech will be corrected are false. In particular, as previously discussed, cases traditionally assume that potentially misleading speech will be corrected either by another source of speech, or, alternatively, by a disclaimer. However, as will be explained, neither can combat alleged facts presented by a self-interested company in the unique prescription drug marketplace. In addition, although commercial speech case law generally does not focus on how persuasive the speech is, that presumption may be less justified in the unique circumstance of off-label drug promotion when there is no contrary speech and the potential public health harm is severe.

Additional information, whether from a source other than the self-interested company or in the form of a disclaimer, is unlikely to make potentially misleading information from such companies no longer misleading. As noted earlier, disclaimers are ineffective at minimizing confusion, even for well-educated audiences such as scientists. In addition, when a new drug is first introduced, and for a number of years after that, there is only *one* company that has information to speak about this drug.<sup>330</sup> Accordingly, unlike the typical market that commercial speech law presumes, where there can be a marketplace of *different* ideas, the abnormal pharmaceutical market unduly represents the views of the industry. Furthermore, as noted in Part II, doctors are vulnerable to being misled by pharmaceutical marketing—and may continue to improperly rely on marketing even in the face of contrary evidence. This is consistent with the fact that studies show repeated information is more likely to be considered true.<sup>331</sup> Moreover, independent research typically results in peer-reviewed articles that are inherently less accessible than detailing and also not as likely to be repeated as commercial marketing messages. Subsequent independent information will also be considered less due to the cognitive bias of anchoring, whereby initial information tends to be the basis upon which subsequent information is perceived. So, any initial misinformation is not truly corrected by another source of speech.

In addition, the potential to mislead a doctor into prescribing a drug for an unapproved use has serious public health consequences but little of the traditional

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specific uses); *supra* Section I.C (noting that there is no direct regulation of off-label uses, but, rather, liability for introducing misbranded drugs based on any indication of drug use that has not been FDA approved).

329. In re *R.M.J.*, 455 U.S. at 202.

330. This is likely since new drugs are typically patented, and patent rights give their owner the right to exclude all others from making or selling the same thing during the term of a patent.

331. See *supra* text accompanying notes 145–147.

First Amendment benefits with respect to promoting democratic principles.<sup>332</sup> Commercial marketing of drugs is unlikely to promote debate on public policy. The sole goal of drug marketing is to increase sales. Since there is already extensive skepticism concerning the value of commercial marketing for uses of drugs that are entirely FDA approved, marketing of uses *not* approved by the FDA should be cautiously considered since these are associated with more adverse effects. As noted earlier, the potential harms may be serious. Although government interests play a role in evaluation of the *Central Hudson* factors for potentially misleading speech, recognizing that stated policy concerns about misleading speech have some similarities with the area of prescription drug promotion is also important in considering how to address issues.

#### IV. AN INFORMED APPROACH TO DRUG ADVERTISING AND DEVELOPMENT

This Part proposes possible solutions to directly address the implications of the previously unveiled and debunked schemas. Section A focuses on legal steps to correct the current undue influence of schemas in commercial speech jurisprudence. Section B goes beyond the legal realm to suggest structural changes to minimize the impact of schemas.

##### *A. Aligning First Amendment Law and Policy with Reality*

This Section proposes several changes to commercial speech law to better recognize that the current lopsided marketing of drugs to doctors results in their being misled, even though they are dangerously unaware of this. There are four specific changes to the law that are recommended. First, courts should recognize that “potentially” misleading information is different than “truthful and non-misleading” information and treat it *differently* as a matter of law in evaluating commercial speech; specific factors are provided to guide courts on how to provide an appropriate

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332. See *Rosenberger v. Rector & Visitors of Univ. of Va.*, 515 U.S. 819, 831 (1995); *Hustler Magazine v. Falwell*, 485 U.S. 46, 55 (1988); see also TAMARA R. PIETY, *BRANDISHING THE FIRST AMENDMENT: COMMERCIAL EXPRESSION IN AMERICA* 165–85 (2012) (raising issues concerning protection of commercial speech in the context of promoting democracy); Robert Post, *The Constitutional Status of Commercial Speech*, 48 UCLA L. REV. 1, 4, 49 (2000) (noting that whereas the First Amendment bars the state from suppressing public discourse due to democratic governance, this policy issue does not apply to commercial speech that is intended instead to focus on promoting information); *supra* notes 100–109 and accompanying text (explaining different treatment of commercial speech versus noncommercial speech). Of course, there are some that believe that commercial speech can nonetheless be tied to democratic self-governance. *E.g.*, Martin H. Redish, *Commercial Speech, First Amendment Intuitionism and the Twilight Zone of Viewpoint Discrimination*, 41 LOY. L.A. L. REV. 67, 81 (2007) (“[S]peech concerning commercial products and services can facilitate private self-government in much the same way that political speech fosters collective self-government.”); Daniel E. Troy, *Advertising: Not “Low Value” Speech*, 16 YALE J. ON REG. 85 (1999) (challenging the notion that commercial information or advertising is less valuable than other forms of speech).

balance between promoting First Amendment protections while still recognizing the possible harms of such information. Second, the burden of proof should be shifted regarding disclaimers; rather than have the FDA prove that information would be misleading, the burden should be on the company to establish that a disclaimer will *not* be misleading. Third, FDA guidance should be reevaluated and informed by cognitive biases. Fourth, courts should defer more to FDA decisions regarding whether information is potentially misleading.

### 1. An Informed Treatment of Potentially Misleading Information

Whereas current First Amendment law treats completely truthful and potentially misleading information as equivalent as a matter of law, these two types of information should be legally distinct—and treated as such when evaluating the *Central Hudson* factors.<sup>333</sup> It is a legal fiction that completely truthful and potentially misleading information are the same. Accordingly, if information is potentially misleading, the government should be given more flexibility in regulating that speech since it has a higher likelihood to mislead. In addition, courts should consider that the FDA has a substantial interest in regulating potentially misleading information that has important public health consequences. This is particularly true in the case of off-label uses that are often not scientifically supported and can result in negative public health outcomes.

Embracing a different treatment for potentially misleading information would help to avoid oddities like *Caronia* where not only was the information not truthful, but the court relied on statements in prior case law that seem questionable with regard to information that is potentially misleading. For example, the *Caronia* majority cited prior Supreme Court precedent that a ban on “truthful and non-misleading” speech rests “solely on the offensive assumption that the public will respond ‘irrationally’ to the truth.”<sup>334</sup> While it may seem “offensive” that individuals respond irrationally to the truth, cognitive bias studies consistently indicate that individuals often do *not* respond rationally.<sup>335</sup> In addition, pharmaceutical marketing favors misrepresentation that is *necessarily* potentially misleading. Unlike other commercial speech challenges involving facts that can be easily verified, such as advertised prices, off-label marketing is a situation where the alleged facts cannot be verified since the only source of information is the self-interested company.<sup>336</sup>

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333. Given the cognitive biases at issue and serious public health risks implicated, there could be an argument for presuming that all marketing of off-label uses should be presumed *actually* misleading unless proven otherwise. After all, pharmaceutical marketing often involves alleged facts for which a court cannot readily assess validity. However, recognizing that this would seem to give the government a complete free pass to bar speech that runs totally contrary to First Amendment jurisprudence. This Article instead makes the more modest suggestion that potentially misleading information be viewed more skeptically.

334. *United States v. Caronia*, 703 F.3d 149, 166–67 (2d Cir. 2012) (quoting *Liquormart, Inc. v. Rhode Island*, 517 U.S. 484, 503 (1996) (striking down ban on price advertisement of alcohol)).

335. See *supra* Section II.A.2 (explaining a number of cognitive biases that result in individuals maintain incorrect beliefs).

336. Moreover, even with an advertisement about prices for attorney services, not all

Treating potentially misleading information differently than actually truthful and non-misleading information would likely also have been beneficial in *Amarin*. The court stated that the FDA “argues only that the claim is ‘potentially misleading,’” as if there are no possible harms with potentially misleading doctors on an issue that impacts public health.<sup>337</sup> Of course, the statement is consistent with current case law. However, some have questioned whether a key claim the court considered truthful and unlikely to mislead even had any factual basis.<sup>338</sup> In particular, the claim that there is “supportive but not conclusive research” that the drug at issue “may reduce the risk of coronary heart disease” has been suggested as equivalent to saying that it “may or *may not* reduce the risk.”<sup>339</sup> In other words, *Amarin*’s statement is “true” in the sense that it has relatively little factual content such that its content is not affirmatively false. Nonetheless, it could still be potentially misleading, which the court did not actually consider since it did not need to under current law that treats potentially misleading information as equivalent to completely nonmisleading and truthful information. However, given the lack of actual sophistication of doctors, there is a potential to mislead.

Of course, the question is how a court should assess whether commercial speech has the potential to mislead. There are two key factors that courts can and should consider whether information is potentially misleading: (1) whether the commercial information can be verified by at least one other source, and especially whether that source is objective and reliable; and (2) the societal cost of misinformation, including the scope of public health harm. The existence of at least one should be considered by a court in coming to the legal determination that information is potentially misleading. Each of these factors will be briefly explained.

An initial issue is whether the commercial speech can be verified by at least one other source, and whether such source(s) are objective and reliable. Importantly, it is essential to look beyond merely whether the source is a peer-reviewed journal article because of previously noted problems with the peer-reviewed articles, including that the industry may have undue influence with these articles. In other words, contrary to prior cases, courts should not assume that a peer-reviewed journal article is objective and unbiased. In addition, sometimes peer-reviewed journals will not even be necessary to find that the commercial information is not accurate and thus has the potential to mislead. For example, in *Caronia*, there was contrary evidence to the commercial speech concerning off-label use of the strongest type of weight—an FDA black box warning specifically cautioning *against* the proposed use.<sup>340</sup>

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justices agreed that such advertisements are not misleading. *See* *Bates v. State Bar of Ariz.*, 433 U.S. 350, 386 (1977) (Burger, C.J., concurring in part, and dissenting in part) (noting skepticism that legal services can be generally considered “standardized” such that advertising is not misleading); *id.* at 391 (Powell & Stewart, JJ., concurring in part, and dissenting in part) (noting that advertising of legal services has “long been thought . . . inevitably . . . misleading because such services are individualized”).

337. *Amarin Pharma, Inc. v. FDA*, 119 F. Supp. 3d 196, 235 (S.D.N.Y. 2015).

338. *See* Spencer Phillips Hey & Aaron S. Kesselheim, *An Uninformative Truth: The Logic of Amarin’s Off-Label Promotion*, PLoS MED., Mar. 2016, at 2.

339. *Id.*

340. *Caronia*, 703 F.3d 149 at 155.

Another important issue is the public health and societal cost of the misinformation. For example, in *Caronia*, encouraging off-label use that is subject to a black box warning could have tragic consequences that should have strong weight in concluding information is potentially misleading. However, this factor should not be limited to considering only tragic consequences. If the commercial speech would encourage avoiding other treatments, especially ones known to be effective *and* less expensive, that would also impose a societal cost in terms of unnecessary expense. So, for example, with a drug that would not likely result in serious public health harm, such as the purified fish oil sold by Amarin, the desired commercial speech concerning an unapproved use could still be considered potentially misleading if it would impose unnecessary costs for the drug without substantial benefit.

## 2. A Modified Burden on Disclaimers

An important change to the law that is well supported by empirical data is to fundamentally change the burden of proof regarding disclaimers before considering that a disclaimer is a less restrictive alternative to barring potentially misleading speech. As discussed earlier, courts currently *presume* that disclaimers will be effective in minimizing confusion and place the burden on the party seeking to restrict speech, such as the FDA, to show that the disclaimer will confuse. Moreover, some courts require that this showing be grounded in empirical evidence.<sup>341</sup> However, empirical evidence shows that disclaimers actually are not understood by consumers.<sup>342</sup> Case law should comport with actual evidence of how consumers process, or, more appropriately, fail to process disclaimers.<sup>343</sup> In particular, drug companies should have the burden of establishing why a disclaimer would be effective in minimizing the possibility of being misled *before* a court can consider that as a viable less speech-restrictive alternative. If a company cannot establish that a disclaimer will actually make its proposed speech less confusing or misleading, then a court can more easily find government regulation, such as barring off-label marketing, to be narrowly tailored since a disclaimer would *not* be a true alternative. Admittedly, permitting a company to speak with a disclaimer is always less speech restricting, but the current presumption that a disclaimer is *effective* at minimizing confusion is flawed.

The proposed burden shift would help address oddities in prior cases. For example, in *Caronia*, the company would need to explain how a disclaimer would adequately protect doctors from being misled. In other words, *Caronia* would be forced to argue what type of disclaimer could guard against its representative asserting that off-label use was not harmful for an elderly patient when that exact use

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341. See, e.g., *Whitaker v. Thompson*, 248 F. Supp. 2d 1, 13 (D.D.C. 2002).

342. See *supra* Section II.C.2.

343. In the context of trademark infringement, courts have sometimes recognized that consumers do not necessarily read disclaimers based on similar studies based on consumer psychology. See Jacob Jacoby & Robert Lloyd Raskopf, *Disclaimers in Trademark Infringement Litigation: More Trouble than They Are Worth?*, 76 TRADEMARK REP. 35 (1986); Gita Venkataramani Johar & Carolyn J. Simmons, *The Use of Concurrent Disclosures to Correct Invalid Inferences*, 26 J. CONSUMER RES. 307 (2000).

was subject to a black box warning. Not only does this seem like a tall order, but given prior studies showing that doctors are not always aware of black box warnings on other products, it is questionable that the black box warning or any other disclaimer could counteract the more easily accessible information provided in detailing.

### 3. More Judicial Deference to FDA Evaluation

Courts should also be more deferential to FDA determinations concerning whether scientific information is either misleading or potentially misleading, or at least no longer require the FDA to provide empirical evidence that a disclaimer will confuse consumers. As noted earlier, there is extensive literature showing that disclaimers are ineffective. This is obviously relevant to any litigation regarding marketing of off-label uses, as well as marketing of products to consumers such as dietary supplements.<sup>344</sup> This is not to suggest that courts should accept FDA assertions at face value without any inquiry. However, the current standards seem premised on the more information schema. For example, courts have suggested that information can only be banned as actually misleading if there is no empirical support at all, or alternatively, only one to two studies that support a claim *in addition* to empirical evidence that an additional disclaimer would still result in consumer confusion.<sup>345</sup> This might be relevant to whether information is actually misleading, but information could be potentially misleading if only a minority of studies, even if more than one to two in total, support a claim.

Although courts routinely evaluate scientific information in general, these cases show that courts are vulnerable to the more information and sophisticated doctor schemas. In contrast, the FDA has not been vulnerable to these positions. To the contrary, the FDA's original position of limiting companies from distributing peer-reviewed articles to doctors for fear of the potential to mislead shows that the FDA does not embrace either position. And, as discussed earlier, the FDA's original position is now empirically supported. On some level, courts recognize that they are less equipped to evaluate key information. For example, although the judge in *Amarin* evaluated a number of statements for alleged truthfulness, at the actual hearing he admitted: "You're talking to somebody who has difficulty using a toaster . . . I'm the last person who should opine on this."<sup>346</sup> In addition, a judge in a single

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344. Of course, the context in which the FDA may be opining on whether information is potentially or actually confusing will be different. For example, since the FDA does not review off-label uses, it is only in the context of a First Amendment challenge, such as *Amarin*, that this would be likely. In contrast, the FDA regularly opines on whether claims concerning dietary supplements and food products are potentially confusing when manufacturers of such products submit proposed health claims for FDA review to ensure that there is "significant scientific agreement" in support of the claim. See 21 U.S.C. § 343(r)(3)(B)(i) (2012) (health claims on food); *id.* § 343(r)(5)(D) (health claims on dietary supplements); see also 21 C.F.R. § 101.14(c) (2017) (standard of FDA approval premised on totality of publicly available scientific evidence and significant agreement among experts that there is evidence in support of the claim); *id.* § 101.14(a)(1) (defining health claim that requires FDA approval).

345. *E.g.*, *Whitaker*, 248 F. Supp. 2d at 10.

346. Amy Kapczynski, *Free Speech and Pharmaceutical Regulation—Fishy Business*, 176



case will not have the same depth of experience as the FDA and could be persuaded by information that may not be scientifically valid.

Recognizing and respecting FDA expertise is an important and timely issue given proposals to remove traditional judicial deference to all agency determinations generally, which would also impact the FDA. In particular, in 2017, the House passed a bill to overturn the common-law principle of “*Chevron* deference,”<sup>347</sup> which arose from the 1984 Supreme Court case, *Chevron v. Natural Resources Defense Council*.<sup>348</sup> Under the *Chevron* deference, if a law passed by Congress is silent or ambiguous with respect to an issue, courts should defer to agency interpretation unless it is unreasonable (i.e., “arbitrary, capricious, or manifestly contrary to the statute”).<sup>349</sup> Accordingly, courts are not to substitute their view for that of the agency, even if another interpretation is reasonable. Although the legislation applies to agencies’ interpretations of all statutes, and has already been criticized, the schemas revealed in this article provide additional report for opposing such legislation, which is currently under consideration by the Senate.<sup>350</sup> This legislation would make the situation even worse than it currently is.

#### 4. Reevaluating FDA Guidance

In addition, the FDA should carefully consider existing cognitive biases if it considers further revising its existing guidelines regarding pharmaceutical marketing of off-label uses. The FDA has already relaxed the guidelines in light of pressure after judicial decisions such as *Caronia* and *Amarin*.<sup>351</sup> However, although the FDA

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J. AM. MED. ASS’N INTERNAL. MED. 295, 295 (2016) (quoting Transcript of Preliminary Injunction Hearing at 79, *Amarin Pharma, Inc. v. FDA*, 119 F. Supp. 3d 196 (S.D.N.Y. 2015) (No. 15 Civ.V 3588 (PAE))).

347. H.R. 5, 115th Cong. (2017–2018). In addition, it passed through the committee phase of the Senate. S. 951, 115th Cong. (2017).

348. *Chevron, U.S.A. Inc. v. Natural Res. Def. Council, Inc.*, 467 U.S. 837 (1984).

349. *Id.* at 844; see also Thomas A. Lorenzen & Sharmistha Das, *The Decline of Deference: Is the Supreme Court Pruning Back the Chevron Doctrine?*, TRENDS: ABA SEC. OF ENV’T, ENERGY, & RESOURCES NEWSL., Sept./Oct. 2015.

350. For critiques of proposed legislation, see, for example, Jonathan J. Darrow, Erin C. Fuse Brown & Aaron S. Kesselheim, *The Regulatory Accountability Act of 2017 – Implications for FDA Regulation and Public Health*, 378 NEW ENG. J. MED. 412 (2018); William Funk, *Requiring Formal Rulemaking Is a Thinly Veiled Attempt to Halt Regulation*, REG. REV. (May 18, 2017), <https://www.theregreview.org/2017/05/18/funk-formal-rulemaking-halt-regulation> [<https://perma.cc/TJH7-ANWJ>].

351. In June 2018, the FDA issued two guidance documents that expand the scope of permissible corporate communications beyond its proposed 2017 guidelines. See *supra* note 81. The guidance documents were long anticipated. See, e.g., GIBSON DUNN, 2017 YEAR-END FDA AND HEALTH CARE COMPLIANCE AND ENFORCEMENT UPDATE – DRUGS AND DEVICES (2018) (noting that the FDA had not provided updated guidance as of January 2018 after two years of anticipation); ELIZABETH RICHARDSON, HEALTH AFFAIRS, HEALTH POLICY BRIEF: OFF-LABEL DRUG PROMOTION. DRUG COMPANIES ARE LARGELY PROHIBITED FROM PROMOTING A DRUG FOR USES THAT HAVE NOT BEEN APPROVED BY THE FOOD AND DRUG ADMINISTRATION (2016) (noting that the FDA had announced that it would be providing new guidance in 2016).

guidelines may seem consistent with these decisions, even the prior 2014 guidelines concerning the safe harbor from prosecution for misbranding permitted action that cognitive bias studies suggest exposes doctors to undue influence. For example, since 2014, after the FDA capitulated to a prior challenge, companies can share peer-reviewed articles supporting off-label use with doctors contrary to long-standing FDA concerns that recent studies show is now justified;<sup>352</sup> in particular, there are recognized problems with the publication process that tend to favor publication of positive results—even before considering that drug companies may be selectively presenting only supportive articles.<sup>353</sup> In addition, even though doctors know at the time that companies show them articles that are likely self-selected, the articles may still be unduly persuasive. Over time, doctors may forget what information they learned from the biased source and simply remember the information that gets repeated, as it may be through multiple articles, and erroneously assume that it is true.<sup>354</sup> In other words, contrary to the 2014 FDA guidance documents permitting companies to share peer-reviewed articles on off-label uses, the FDA's original instinct to bar companies from sharing such information for fear of undue influence of unsupported information was correct. It seems unlikely that the FDA will retreat from the increasingly expanded safe harbor for off-label marketing practices. Nonetheless, recognizing that existing case law may be inconsistent with empirical evidence should give the FDA pause before further capitulating to industry demands.

### *B. Suggestions for Structural Reforms*

This Section sketches suggestions for structural reforms to address the issues raised. This Section first suggests increasing awareness of the extent and effectiveness of marketing influence to minimize the sophisticated doctor schema. This Section also proposes specific actions to limit marketing influences from self-interested companies by both limiting the extent of marketing, as well as promoting independent and accessible information. Finally, this Section argues that the data revealed here support more extensive changes to the current system of drug development reliant on profit-based companies.

#### 1. Increase Awareness

To combat the sophisticated doctor schema, an important initial step is to increase awareness of marketing influences on doctors. Lack of awareness is likely the reason most doctors believe they are not adversely influenced by detailing and improperly assume they are able to glean relevant information.<sup>355</sup> This Section focuses primarily on educating doctors who are being targeted with advertisements and for whom there are existing channels to provide such information. Judges need to be informed as

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352. For example, the *Caronia* majority quoted from the FDA's own guidelines that the FDA recognized the value of truthful and nonmisleading scientific information on unapproved uses, such as through scientific journals. *United States v. Caronia*, 703 F.3d 149, 166–67 (2d Cir. 2012).

353. See *supra* Section I.B.

354. See *supra* Section II.A.2.

355. Fischer, *supra* note 172, at 796.

well, although this can be done on a case-by-case basis through briefs by parties, as well as amici.

Increasing awareness of the sophisticated doctor schema is consistent with existing concerns. For example, the U.S. Accreditation Council for Continuing Medical Education has expressed concern that residents learn how promotional activities can influence their prescribing information and the World Health Organization has urged countries to include information on commercial marketing strategies in formal training.<sup>356</sup> In addition, some academic institutions have also limited promotional activity,<sup>357</sup> and some doctors already turn away salespeople.<sup>358</sup> However, more consistent revelation of marketing influences is important not only in medical schools, but also through continuing medical education, since doctors of all ages are vulnerable to marketing.

Increased awareness can build upon the work of Healthy Skepticism, an international organization that aims to better inform doctors about their susceptibility to subtle techniques used by advertisers.<sup>359</sup> They have already created training modules about how people are vulnerable to persuasion,<sup>360</sup> and also have training to reduce overconfidence bias, including the mistaken belief by many doctors that without any training, they can easily distinguish misleading claims from justified ones.<sup>361</sup> Some of these modules could be easily incorporated into medical education (whether initial or continuing). There have also been promising results for better educating doctors and residents to recognize that they are vulnerable to marketing by limiting their overconfidence.<sup>362</sup> For example, one established method is to expose

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356. ACCREDITATION COUNCIL FOR CONTINUING GRADUATE MED. EDUC., PRINCIPLES TO GUIDE THE RELATIONSHIP BETWEEN GRADUATE MEDICAL EDUCATION, INDUSTRY, AND OTHER FUNDING SOURCES FOR PROGRAMS AND SPONSORING INSTITUTIONS ACCREDITED BY THE ACGME (2011), <https://www.acgme.org/Portals/0/PFAssets/PublicationsPapers/GME-Funding-Industry-Other-Sources.pdf> [<https://perma.cc/HZ2C-J6R4>]; BARBARA MINTZES, WORLD HEALTH ORG. & HEALTH ACTION INT'L, EDUCATIONAL INITIATIVES FOR MEDICAL AND PHARMACY STUDENTS ABOUT DRUG PROMOTION: AN INTERNATIONAL CROSS-SECTIONAL SURVEY (2005).

357. *E.g.*, David L. Coleman, *Establishing Policies for the Relationship Between Industry and Clinicians: Lessons Learned from Two Academic Health Centers*, 83 ACAD. MED. 882 (2008); Larkin et al., *Physician Prescribing*, *supra* note 64; *see also* PEW CHARITABLE TR., CONFLICT-OF-INTEREST POLICIES FOR ACADEMIC MEDICAL CENTERS 12 (2013) (recommending barring pharmaceutical representatives as one type of best practice).

358. *E.g.*, Robert Lowes, *More Physicians Saying 'No Drug Reps Allowed'*, MEDSCAPE (Sept. 13, 2016), <https://www.medscape.com/viewarticle/868748> [<https://perma.cc/CY5G-XSEJ>] (noting that approximately thirty-five percent turn away salespeople).

359. *See* Mansfield, *Healthy Skepticism*, *supra* note 132, at 644.

360. *Id.* at 645.

361. *See id.* The organization also aims to disabuse doctors of other unsupported schemas that the industry promotes, such as the fiction that newer drugs are in general better, in contrast to the reality where only about three percent are major advances. *Id.*

362. *See* Peter R. Mansfield, Joel Lexchin, Leana S. Wen, Luisella Grandori, Christopher P. McCoy, Jerome R. Hoffman, Joana Ramos & Jon N. Jureidini, *Educating Health Professionals About Drug and Device Promotion: Advocates' Recommendations*, PLOS MED., Nov. 2006, at 1988 [hereinafter Mansfield et al., *Educating Health*]; *see* Sagarin et al., *supra* note 126.

individuals to a standard sales technique, allow individuals to express any beliefs, and then debunk them, as well as explain what misleading techniques were used.<sup>363</sup> Importantly, this has been shown to reduce overconfidence in feeling “skilled” at critically appraising information from health representatives.<sup>364</sup>

In addition, informing doctors of the benefits of limiting industry interaction, coupled with how to substitute the perceived benefits of industry marketing, would also be valuable. For example, doctors frequently state that they find detailing a convenient way both to learn about drugs and get drug samples for their patients, while also praising the social and informative aspects of lunches paid for by companies.<sup>365</sup> However, some of these benefits are illusory. One family medicine practice that took an inventory of free drug samples found that few were “first-line” drugs for most common illnesses, and less expensive alternatives were available for a majority.<sup>366</sup> In addition, for a relatively low cost, the practice maintained educational group lunches that were not influenced by marketing and instead provided educational information about both new and old drugs based on peer-reviewed articles.<sup>367</sup> Although some doctors were initially resistant and skeptical of removing all industry influence, seeing actual data regarding number of visits and samples was helpful.<sup>368</sup>

This example illustrates that it may be important not only to make doctors aware of the influence of marketing, but perhaps also to increase awareness with their own *peers*. As noted earlier, doctors can be skeptical of those outside their own circles. Also, there are some doctors, albeit a minority, that do recognize vulnerability to marketing. Accordingly, there should be a pool of doctors that can assist in increasing awareness among all doctors. In addition, if medical schools can follow the lead of many academic centers in not only limiting pharmaceutical interaction, but also educating students about their vulnerability, this could strongly facilitate increased knowledge for a new generation of doctors.

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363. Mansfield et al., *Educating Health*, *supra* note 362, at 1989.

364. Michael S. Wilkes & Jerome R. Hoffman, *An Innovative Approach to Educating Medical Students About Pharmaceutical Promotion*, 76 ACAD. MED. 1271, 1274 (2001).

365. E.g., David Evans, Daniel M. Hartung, Denise Beasley & Lyle J. Fagnan, *Breaking Up is Hard to Do: Lessons Learned from a Pharma-Free Practice Transformation*, 26 J. AM. BD. FAM. MED. 332, 334 (2013). Even doctors that consider information from representatives to be biased may enjoy detailing visits for the physical relationship or for gifts received from doctors. Fischer et al., *supra* note 172, at 797–98; Spiller & Wymer, *supra* note 171, at 94 (internal citations omitted). In addition, many doctors consider the detailing useful information. See *supra* note 171 and accompanying text; see also Sorrell v. IMS Health Inc., 564 U.S. 552, 578 (2011) (noting that doctors find detailing “very helpful”).

366. Evans et al., *supra* note 365, at 334.

367. *Id.* at 334, 336 (noting that since some providers were initially resistant to terminating free samples and all visits by pharmaceutical representatives, intermediate steps were taken to transition providers and ultimately providers could see that there were cheaper options available).

368. Some noted that they needed industry information to be current and there would be negative social harm, but eventually all agreed that this was a positive step. *Id.* at 336.

## 2. Beyond Conflicts of Interest - Reconsidering Drug Samples and Gifts

Although industry influence resulting in conflicts of interest prompted enactment of the Sunshine Act, the cognitive biases discussed here provide additional reasons to be concerned about manipulative marketing not only with off-label uses of drugs, but for all prescription drugs. After all, the industry uses the same types of marketing for all uses of prescription drugs.

Importantly, whereas the Sunshine Act was promulgated under the theory that more transparency would limit industry influence since doctors would be hesitant to accept money they would need to disclose, this legislation inherently fails to address key cognitive biases that still subject doctors to the influence of industry marketing. For example, the Sunshine Act seems to assume that smaller value items, such as drug samples and gifts under \$100 have no impact, and thus exempts these from disclosure.<sup>369</sup> However, both of these types of items can and do have an impact—even though the law does not currently recognize this and doctors assume that there are no dangers.<sup>370</sup> The industry invests over \$5 billion a year on these practices, which yield profitable outcomes for companies.<sup>371</sup> Studies consistently show that samples impact prescriptions.<sup>372</sup> This makes sense given the cognitive bias of availability that impacts everyone, including doctors; since samples are available, doctors are naturally inclined to think about them for prescribing.<sup>373</sup>

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369. Patient Protection & Affordable Care Act, Pub. L. No. 111-148, § 1128G(e)(10)(B)(i)-(ii), 124 Stat. 119, 696 (codified at 42 U.S.C. § 18001 (2012)).

370. See Allan S. Brett, Wayne Burr & Jamaluddin Moloo, *Are Gifts from Pharmaceutical Companies Ethically Problematic?: A Survey of Physicians*, 163 ARCHIVE INTERNAL MED. 2213 (2003); Steinman et al., *supra* note 174. Although some scholars have previously recognized the impact of small gifts to influence doctors, arguments that these resulted in conflicts of interests perhaps led to the improper assumption that they are not of concern. See, e.g., Susan Chimonas, Troyen A. Brennan & David J. Rothman, *Physicians and Drug Representatives: Exploring the Dynamics of the Relationship*, 22 J. GEN. INTERNAL MED. 184 (2007); Jason Dana & George Lowenstein, *A Social Science Perspective on Gifts to Physicians from Industry*, 290 J. AM. MED. ASS'N 252 (2003); Wazana, *supra* note 20.

371. E.g., *Persuading the Prescribers: Pharmaceutical Industry Marketing and Its Influence on Physicians and Patients*, PEW (Nov. 11, 2013), <https://www.pewtrusts.org/en/research-and-analysis/fact-sheets/2013/11/11/persuading-the-prescribers-pharmaceutical-industry-marketing-and-its-influence-on-physicians-and-patients> [https://perma.cc/APM7-B6G5].

372. E.g., John M. Boltri, Elizabeth R. Gordon & Robert L. Vogel, *Effect of Antihypertensive Samples on Physician Prescribing Patterns*, 34 FAMILY MED. 729 (2002); Lisa D. Chew, Theresa S. O'Young, Thomas K. Hazlet, Katharine A. Bradley, Charles Maynard & Daniel S. Lessler, *A Physician Survey of the Effect of Drug Sample Availability on Physicians' Behavior*, 15 J. GEN. INTERNAL MED. 478 (2000); Fickweiler et al., *supra* note 172, at 3; Adriane Fugh-Berman & Shahram Ahari, *Following the Script: How Drug Reps Make Friends and Influence Doctors*, PLoS MED., Apr. 2007, at 621, 624.

373. In addition, direct to consumer advertising may prompt consumers to specifically request brand name drugs. Richard L. Kravitz, Ronald M. Epstein, Mitchell D. Feldman, Carol E. Franz, Rachman Azari, Michael S. Wilkes, Ladson Hinton & Peter Franks, *Influence of Patients' Requests for Direct-to-Consumer Advertised Antidepressants: A Randomized Controlled Trial*, 293 J. AM. MED. ASS'N 1995, 1998-99 (2005) (reporting that for some types of issues, doctors were more likely to prescribe the specific drug requested by a patient) as a

Doctors who embrace the sophisticated doctor schema may believe that they are invulnerable to influence from these low-budget items and also provide justifications that are not consistent with reality. For example, doctors often report that samples make patients happy, or result in lower costs especially for low-income patients,<sup>374</sup> and that receiving them has no impact on their prescriptions.<sup>375</sup> However, in fact, data show that drug samples are typically provided to high, rather than low-income patients and also ironically lead to higher costs, since (1) typically a patient will need more than the initial sample and (2) samples are inevitably of high-priced patented drugs.<sup>376</sup> Furthermore, studies indicate that patients actually disapprove of both samples and gifts.<sup>377</sup>

Given this reality, the question is what the next step should be. An easy first step would be informing doctors of these data more broadly, perhaps through continuing medical education. In particular, informing doctors of colleagues who have successfully taken this step and have come to see the benefits, including those who were initially skeptical, might be helpful.<sup>378</sup> One small practice group has provided a template for how a group can voluntarily extricate itself from such pharmaceutical marketing.<sup>379</sup> Some doctors may still be resistant to believing the data, given their preexisting biases. Accordingly, a more drastic step would be to legally bar companies from providing drug samples. Of course, this is a major change that would

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result of advertising); Michael S. Wilkes, Robert A. Bell & Richard L. Kravitz, *Direct-to-Consumer Prescription Drug Advertising: Trends, Impact, and Implications*, 19 HEALTH AFF. 110, 118 (2000) (finding that in one survey, nineteen percent of people asked for a specifically advertised drug). When consumers ask for such drugs, doctors likely have samples since companies use both methods to market drugs. Gagnon & Lexchin, *supra* note 53, Table 1 (noting expenditures on detailing as well as advertising to consumers).

374. E.g., Fischer et al., *supra* note 172, at 797 (noting that doctors claimed that samples make patients happy and even that patients expect samples); Tim Lahey, *The High Costs of "Free" Drug Samples*, CLINICAL & TRANSLATIONAL GASTROENTEROLOGY, 2014, at 1 (noting that some doctors believe samples benefit low-income patients).

375. See, e.g., Richard F. Adair & Leah R. Holmgren, *Do Drug Samples Influence Resident Prescribing Behavior? A Randomized Trial*, 118 AM. J. MED. 881, 883 (2005); Brian Hodges, *Interactions with the Pharmaceutical Industry: Experiences and Attitudes of Psychiatry Residents, Interns and Clerks*, 153 CAN. MED. ASS'N J. 553, 558 (1995); Dana Katz, Arthur L. Caplan & Jon F. Merz, *All Gifts Large and Small: Toward an Understanding of the Ethics of Pharmaceutical Industry Gift-Giving*, 10 AM. J. BIOETHICS 11, 12 (2010); Steinman et al., *supra* note 174, at 555.

376. See Sarah L. Cutrona, Steffie Woolhandler, Karen E. Lasser, David H. Bor, Danny McCormick & David U. Himmelstein, *Characteristics of Recipients of Free Prescription Drug Samples: A Nationally Representative Analysis*, 98 AM. J. PUB. HEALTH 284, 285–87 (2008); Lahey, *supra* note 374, at 1.

377. Lynn Eaton, *Readers Want Transparency in Link Between Doctors and Drug Firms*, 326 BRIT. MED. J. 1352, 1352 (2003); Robert V. Gibbons, Frank J. Landry, Denise L. Blouch, David L. Jones, Frederick K. Williams, Catherine R. Lucey & Kurt Kroenke, *A Comparison of Physicians' and Patients' Attitudes Toward Pharmaceutical Industry Gifts*, 13 J. GEN. INTERNAL MED. 151, 152–53 (1998); James Jastifer & Sarah Roberts, *Patients' Awareness of and Attitudes Toward Gifts from Pharmaceutical Companies to Physicians*, 39 INT'L J. HEALTH SERVS. 405, 411 (2009).

378. Fischer et al., *supra* note 172, at 798.

379. See *supra* notes 365–368 and accompanying text.

likely be vigorously opposed by the well-funded pharmaceutical industry that spends billions a year on promotional activity, with the vast majority being spent on detailing and drug samples, such that it may not be a realistic recommendation in the near future. Nonetheless, doing so is consistent with cognitive bias studies.<sup>380</sup>

### 3. Other Mechanisms to Minimize Public Harm From Schemas

Given the serious potential public health hazards associated with off-label use in addition to the lack of awareness of schemas, additional action could be taken to minimize harm, including mechanisms that would require no change to the First Amendment law or challenging existing schemas held by doctors. In particular, off-label use that is not medically supported could, and arguably should, be limited. This would be consistent with an evidence-based approach to medicine that many suggest is how medicine should be practiced, even if that does not always happen. The existing law governing Medicare payments could be amended to limit payments for off-label use unless it is supported by high-quality evidence *and* what counts as evidence is revisited. After all, current guidelines are fairly permissive and can rely on compendiums<sup>381</sup> that studies have shown to be sometimes not accurate or up to date,<sup>382</sup> as well as medical articles that are not always reliable.<sup>383</sup> Of course, this would likely be strongly opposed by the pharmaceutical industry. Alternatively, private insurance companies could endeavor to modify their reimbursement for unsupported off-label use. Insurance companies have a clear interest in not paying for unnecessary treatment and in recent years have been more strictly limiting payment for drugs with various tiered formularies. The proposed change would be an expansion of the existing approach to not only consider drugs within the same class differently, but also the *use* of the drug. This may be complicated under the existing system where doctors generally do not need to indicate the use for a drug on a prescription. However, electronic medical records make this easier, indicating that this is not impossible.<sup>384</sup>

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380. Gagnon & Lexchin, *supra* note 53, at 29, 31.

381. Medicare covers all “medically accepted indications,” which includes not just FDA-approved indications, but also compendia-based information. 42 U.S.C. § 1396r-8(k)(6) (2012) (defining medically accepted indication for Medicaid to include certain compendia); *see also* 42 U.S.C. § 1396r-8(g)(1)(B)(i) (2012); 42 C.F.R. § 423.100 (2015) (defining Medicare Part D drug with reference to Medicaid definition of medically accepted indication).

382. *E.g.*, Amy P. Abernethy, Gowri Raman, Ethan M. Balk, Julia M. Hammond, Lori A. Orlando, Jane L. Wheeler, Joseph Lau & Douglas C. McCrory, *Systematic Review: Reliability of Compendia Methods for Off-Label Oncology Indications*, 150 ANNALS INTERNAL MED. 336, 341–42 (2009) (finding that compendia do not always link recommendations to evidence and often are not the most current evidence used).

383. Medical literature may also be considered for Medicaid reimbursement, but is not alone adequate except for anticancer treatment. 42 U.S.C. § 1396r-8(g)(1)(B)(ii) (2012); 70 Fed. Reg. 4194, 4228–29 (Jan. 28, 2005) (to be codified at 42 C.F.R. pt. 423); *see also* Jennifer L. Herbst, *How Medicare Part D, Medicaid, Electronic Prescribing, and ICD-10 Could Improve Public Health (But Only if CMS Lets Them)*, 24 HEALTH MATRIX: J. L.-MED. 209, 216 (2014).

384. *See* Eguale et al., *supra* note 96, at 56 (noting that in Quebec documentation of treatment indication is mandatory).

#### 4. Towards More Independent and Accessible Information

A major issue with pharmaceutical marketing is its widespread availability and accessibility, making doctors more likely to rely on it even if they realize it is skewed and not well supported. Even informing doctors that they are relying on the information unduly is not likely to be ideal since studies repeatedly show that all individuals tend to rely on easily accessible information. To counteract industry marketing, not only do different sources of information need to exist, but they need to be as available and accessible as existing marketing. If such independent and accessible information exists when drugs are first introduced, there would be less of a need to train doctors about marketing influences. But, since such independent information currently does not exist, greater awareness is essential, even if the best possible results from that awareness are still suboptimal. Importantly, if the majority, rather than a minority, of doctors were aware of their vulnerability to marketing, perhaps that could help to better protect patients since doctors do consult with peers and seem to generally value peer opinions, as opposed to those outside their profession.

There is already some recognition of the need to develop independent data in the broader medical context. A 2007 study found that less than half of recommended treatments are based on sound science.<sup>385</sup> Since then, Congress has included appropriations to fund comparative effectiveness studies.<sup>386</sup> These studies are essential to complement initial studies done by self-interested drug companies that typically only evaluate a proposed new drug versus a placebo, rather than existing treatments, and also under experimental, rather than typical scenarios. Even in the limited situations where companies compare their drugs to others, the study may be skewed due to different dosages or other modifications. Such maneuvers should arguably be easy for physicians to spot. And, if companies presented all information to doctors, that might be true. However, there is no incentive for companies to do so.

Assuming independent data can be developed, the next step is to make the data easily available and accessible to doctors. One way to do so is to actually mirror the effective drug detailing done by companies with “academic detailing,” whereby scientifically trained individuals with no profit-based agenda are providing information in a one-on-one format that has been shown to be accessible and convenient for doctors.<sup>387</sup> Studies have shown some success in improving care

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385. INST. OF MED. OF THE NAT’L ACADS., *LEARNING WHAT WORKS BEST: THE NATION’S NEED FOR EVIDENCE ON COMPARATIVE EFFECTIVENESS IN HEALTH CARE* 78 (2011) (citing 2007 study).

386. American Recovery and Reinvestment Act, Pub. L. No. 111-5, 123 Stat. 115 (2009); see also Robert Pear, *U.S. to Compare Medical Treatments*, N.Y. TIMES (Feb. 15, 2009), <https://www.nytimes.com/2009/02/16/health/policy/16health.html> [<https://perma.cc/72L7-PAG2>].

387. See Jerry Avorn, *Academic Detailing: “Marketing” the Best Evidence to Clinicians*, 317 J. AM. MED. ASS’N 361 (2017); Michael A. Fischer & Jerry Avorn, *Academic Detailing Can Play a Key Role in Assessing and Implementing Comparative Effectiveness Research Findings*, 31 HEALTH AFF. 2206 (2012). In addition, although academic detailing is likely the most accessible method, even continuing medical education can be made more effective if the traditional pure lecture styles are replaced by more interactive formats that have been found



through academic detailing.<sup>388</sup> Of course, although academic detailing is beneficial, it would be tough to rely on academic detailing *alone* to completely counteract misleading marketing messages, contrary to the presumptions of the *Sorrell* majority opinion. After all, the pharmaceutical industry has substantial funds to promote its own products. Most academic detailing focuses on one or two limited areas. Nonetheless, greater attention to academic detailing is better than none at all. It is also a strategy that has no commercial speech problems, such that some scholars recently suggested it as a strategy to address *Sorrell*.<sup>389</sup>

#### 5. Additional Support for Reconsidering the Drug Development Process

The data presented here also provides additional support for questioning the overall system of drug development, and not simply issues concerning off-label use of drugs. This Article shows that companies have an incentive to promote off-label uses that may not be supported by evidence. However, the problems with drug development and marketing are much more extensive. Not only do companies have an incentive to market off-label uses during the limited term of patent protection to maximize profits, but they also have an incentive to develop the most profitable drugs, which are not necessarily the ones that are most socially desirable.<sup>390</sup> For example, most drugs are developed for relatively wealthy countries that have the ability to pay.<sup>391</sup> This is not a new discovery. Indeed, legislation exists to try to encourage companies to promote drugs that impact smaller classes with a variety of incentives that include tax advantages, as well as commercial exclusivity.<sup>392</sup>

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useful in a wide array of educational contexts.

388. *E.g.*, Avorn, *supra* note 387 (noting that since research started in the 1980s, studies have shown success in improving care in a variety of settings, including controlling use of sedating medications in nursing homes and reducing overuse of antibiotics).

389. George R. Gooch, J. James Rohack & Marisa Finley, *The Moral From Sorrell: Educate, Don't Legislate*, 23 HEALTH MATRIX 237, 262 (2013).

390. *E.g.*, Steven J. Hoffman & Karen So, *Assessing 15 Proposals for Promoting Innovation and Access to Medicines Globally*, 80 ANNALS GLOBAL HEALTH 432, 433 (2014). Some have suggested that since the patent system contributes to this problem, alternatives are needed to encourage socially valuable innovation. *E.g.*, HO, *supra* note 11, at 367–71 (discussing proposals such as a health impact fund, publicly funded clinical trials, and a drug development corporation); UNITED NATIONS, REPORT OF THE UNITED NATIONS SECRETARY-GENERAL'S HIGH-LEVEL PANEL ON ACCESS TO MEDICINES: PROMOTING INNOVATION AND ACCESS TO HEALTH TECHNOLOGIES 7 (2016).

391. This is referred to as the 10/90 gap: less than ten percent of resources are devoted to the health needs of developing countries where over ninety percent of preventable deaths occur. Roderik F. Viergever, *The Mismatch Between the Health Research and Development (R&D) that Is Needed and the R&D that is Undertaken: An Overview of the Problem, the Causes, and Solutions*, 6 GLOBAL HEALTH ACTION 22450, 22450 (2013). This is such a substantial problem that it is included in a “scorecard” of how well pharmaceutical companies are acting in the interest of poorer countries. ACCESS TO MED. FOUND., ACCESS TO MEDICINE INDEX 2018: METHODOLOGY REPORT (2018) (explaining basis for scoring that includes not only research into needs of developing countries, but also providing access to needed medications).

392. Orphan Drug Act, Pub. L. No. 97-414, 96 Stat. 2049 (1982) (codified as amended at

However, the industry has managed to game this well-intended legislation to obtain handsome profits while sometimes also charging exorbitant prices to consumers.<sup>393</sup> In light of these issues, there have been proposals to overhaul the domestic and international system.<sup>394</sup> Admittedly, a major overhaul to the drug development process would be a major change and a complete discussion is beyond the scope of

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21 U.S.C. § 360aa-360ee (2012), 26 U.S.C. § 45C (2012), 42 U.S.C. § 236 (2012)); Council Regulation 141/2000, 2000 O.J. (L 18) 1.

393. *Anticompetitive Abuse of the Orphan Drug Act: Invitation to High Prices: Hearing Before the Subcomm. on Antitrust, Monopolies & Business Rights of the S. Comm. on the Judiciary*, 102d Cong. 198 (1992) (statement of John L. Castello); Jess G. Thoene, *Curing the Orphan Drug Act*, 251 SCI. 1158, 1158 (1991); Dina Gusovsky, *How a Blockbuster Drug Can Become a Subsidized 'Orphan'*, CNBC (Dec. 2, 2015, 11:27 AM), <https://www.cnbc.com/2015/12/01/an-obscure-fda-rule-adding-to-drug-company-profits.html> [<https://perma.cc/3DCX-GSZW>]; Sarah Jane Tribble & Sydney Lupkin, *Drugs for Rare Diseases Have Become Uncommonly Rich Monopolies*, NPR (Jan. 17, 2017, 4:59 AM), <https://www.npr.org/sections/health-shots/2017/01/17/509506836/drugs-for-rare-diseases-have-become-uncommonly-rich-monopolies> [<https://perma.cc/HTQ5-CZEA>]. Indeed, drugs originally approved as orphan drugs have high potential for off-label marketing to expand company profitability. *E.g.*, Marc-André Gagnon, *New Drug Pricing: Does It Make Any Sense?*, 24 PRESCRIBE INT'L 192 (2015); Shannon Gibson, Hamid R. Raziee & Trudo Lemmens, *Why the Shift? Taking a Closer Look at the Growing Interest in Niche Markets and Personalized Medicine*, 7 WORLD MED. & HEALTH POL'Y 3, 15 (2015). There are some proposals to modify the system. *E.g.*, Sarah Jane Tribble, *House Republicans Aim to Yank Tax Credits for Orphan Drugs*, KHN (Nov. 2, 2017), <https://khn.org/news/house-republicans-aim-to-yank-tax-credits-for-orphan-drugs> [<https://perma.cc/RZ3K-WFGL>].

394. *E.g.*, FINKELSTEIN & TEMIN, *supra* note 13; AIDAN HOLLIS & THOMAS POGGE, THE HEALTH IMPACT FUND: MAKING NEW MEDICINES ACCESSIBLE FOR ALL (2008); UNITED NATIONS, REPORT OF THE UNITED NATIONS SECRETARY-GENERAL'S HIGH-LEVEL PANEL ON ACCESS TO MEDICINES: PROMOTING INNOVATION AND ACCESS TO HEALTH TECHNOLOGIES (2016); Tim Hubbard & James Love, *A New Trade Framework for Global Healthcare R&D*, PLOS BIOLOGY, 2004, at 0147. Even relatively modest suggestions, such as changing the law to permit Medicare to reduce prices attract controversy. Medicare Negotiation and Competitive Licensing Act, H.R. 6505, 115th Cong. (2018); Peter Rheinstein, *Gutting Drug Patents Puts Lives at Risk*, NAT'L REV. (Oct. 2, 2018, 6:30 AM), <https://www.nationalreview.com/2018/10/gutting-drug-patents-puts-lives-at-risk> [<https://perma.cc/AZ83-CFRR>]. There are also proposals for drug cost transparency laws that, while not reforming the entire system, aims to at least require accountability; although no federal legislation has passed, some states have been successful. Prescription Drug Price Transparency Act, H.R. 1316, 115th Cong. (2017); Ameet Sarpatwari, Jerry Avorn & Aaron S. Kesselheim, *State Initiatives to Control Medication Costs – Can Transparency Legislation Help?*, 374 NEW ENG. J. MED. 2301 (2016); Zachary Brennan, *Oregon Governor Signs Drug Price Transparency Bill*, REG. AFF. PROF. SOC'Y (Mar. 13, 2018), <https://www.raps.org/news-and-articles/news-articles/2018/3/oregon-bill-on-drug-price-transparency-headed-to-g> [<https://perma.cc/3BZK-764V>]; Ron Lanton, III, *The Current State of Drug Price Legislation*, SPECIALTY PHARMACY TIMES (Nov. 16, 2017), <https://www.specialtypharmacytimes.com/publications/specialty-pharmacy-times/2017/november-2017/the-current-state-of-drug-price-legislation> [<https://perma.cc/RQP2-8GBV>]; Ed Silverman, *Vermont Becomes First State to Require Drug Makers to Justify Price Hikes*, STAT (June 6, 2016), <https://www.statnews.com/pharmalot/2016/06/06/vermont-drug-prices-transparency> [<https://perma.cc/GG2Z-A54K>].

this Article. However, the data in this Article lends further support to arguments that the current system is broken, and more serious attention to fixing it is required.

#### CONCLUSION

The intersection of commercial speech and FDA regulation of unapproved uses of FDA-approved drugs is an important area to commercial drug companies, as well as policy makers concerned about public health. Given recent judicial expansion of commercial speech, as well as pressure on the FDA to further liberalize corporate speech concerning uses without clear scientific foundation, it is important to consider the appropriate balance. This Article has revealed, and debunked, two key schemas prevalent in key cases, as well as among doctors and policy makers. A better understanding of these schemas would inform appropriate changes to commercial speech law to mirror reality. Moreover, these schemas also support more systematic changes to drug development and marketing in favor of an independent and evidence-based system. In addition, the existence of these schemas provide strong support for issues beyond off-label promotion of drugs. In particular, the schemas suggest that the current minimal scrutiny of dietary supplements with a disclaimer may not be wellfounded. Considering that doctors are more sophisticated than consumers and still vulnerable to commercial advertising, the schemas revealed here also suggest that direct-to-consumer advertisement should be more, rather than less, restricted. Although it is unlikely that all of these changes could be made, even understanding the existence and operation of these schemas is an important first step towards an improved understanding that should yield the informed results that all agree are desirable.