



Back to first principles: a new model for the regulation of drug promotion

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ABSTRACT

The US Food and Drug Administration's ('FDA' or the 'Agency') current regulatory framework for drug promotion, by significantly restricting the ability of drug manufacturers to communicate important, accurate, up-to-date scientific information about their products that is truthful and non-misleading, runs afoul of the First Amendment and actually runs counter to the Agency's public health mission. Our article proposes a New Model that represents an initial proposal for a modern, sustainable regulatory framework that comprehensively addresses drug promotion while protecting the public health, protecting manufacturers' First Amendment rights, establishing clear and understandable rules, and maintaining the integrity of the FDA approval process. The New Model would create three categories of manufacturer communications—(1) Scientific Exchange and Other Exempt Communications, (2) Non-Core Communications, and (3) Core Communications—that would be regulated consistent with the First Amendment and according to the strength of the government's interest in regulating the specific communications included within each category. The New Model should address the FDA's concerns related to off-label speech while protecting drug manufacturers' freedom to engage in truthful and non-misleading communications about their products.

KEYWORDS: First Amendment, off-label enforcement, regulatory framework, FDA regulation, drugs and devices, promotion, scientific exchange

I. INTRODUCTION

'We have a saying in medicine, information is power. And the more you know, or anyone knows, the better decisions can be made.' Vermont physician quoted in *Sorrell v. IMS Health Inc.*¹

The history of the FDA's regulation of drug² approval and promotion demonstrates the necessary and delicate balancing act that rests at the core of the Agency's mandate under the Federal Food, Drug, and Cosmetic Act ('FDCA' or the 'Act'): to promote the public health by enhancing patient access to products that are safe and effective for their intended uses.³ FDA's statutory and regulatory framework governing drug labeling and advertising was originally developed more than 50 years ago at a time when methods of drug promotion by manufacturers, and the level of medical information available to healthcare professionals were very different than they are today.⁴

The Agency generally considers any use of a drug, including dosage, patient population, and route of administration that does not conform to the FDA-approved label to be an 'off-label' use.⁵ The FDA's regulatory framework generally prohibits a manufacturer from promoting an off-label use.⁶ FDA and courts have long recognized that healthcare professionals may prescribe a drug for such an off-label use and speak openly about it,⁷ and FDA acknowledges that off-label uses may in some cases constitute the recognized standard of care.⁸ Off-label uses are especially critical for the treatment of oncology, heart disease, AIDS, kidney disease, osteoporosis, and psychiatric illnesses.⁹

¹ *Sorrell v. IMS Health Inc.*, 131 S. Ct. 2653, 2671 (2011).

² In general, the same promotional rules that apply to drugs also apply to biological products licensed under the Public Health Service Act. See 42 U.S.C. § 262(j). For the sake of convenience, this article uses the word 'drug' as shorthand to refer to both drug and biological products.

³ See FDA, *What We Do*, <http://www.fda.gov/aboutfda/whatwedo/> (accessed Apr. 10, 2015).

⁴ See generally Terry S. Coleman, *Origins of the Prohibition Against Off-Label Promotion*, 69 FOOD & DRUG L.J. 161 (2014).

⁵ According to one regulatory preamble from FDA, a new use for an approved drug may include, but is not limited to, a different indication, new dose, new dosing schedule, new route of administration, new age group, patient sub-group not identified in the labeling, different stage of disease, different intended outcome, and effectiveness for a sign or symptom not in the labeling, among others. 63 Fed. Reg. 64556, 64559 (Nov. 20, 1998).

⁶ See Part III, *infra*.

⁷ See, e.g., 21 U.S.C. § 396; 21 C.F.R. § 312.2(d); 48 Fed. Reg. 26,720, 26,733 (June 9, 1983); 37 Fed. Reg. 16,503, 16,503 (Aug. 15, 1972). See *Ass'n of Am. Physicians & Surgeons, Inc. v. FDA*, 226 F. Supp. 2d 204, 206 (D.D.C. 2002) ('[w]hen ... FDA approves a drug, it [is] approve[d] for [a] particular use' but 'the FDCA does not regulate how the drug may be prescribed'); See also *Sigma-Tau Pharms., Inc. v. Schwetz*, 288 F.3d 141, 147 (4th Cir. 2002) (noting 'the longstanding practice of Congress, the FDA, and the courts not to interfere with physicians' judgments and their prescription of drugs for off-label uses').

⁸ E.g., FDA, *Informed Consent Information Sheet: Guidance for IRBs, Clinical Investigators, and Sponsors*, July 2014, at 9, <http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM405006.pdf>; FDA, *Guidance for Industry: 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* Jan. 2009, <http://www.fda.gov/regulatoryinformation/guidances/ucm125126.htm> (hereinafter '2009 Reprints Guidance').

⁹ See Michael Soares, "Off-Label" Indications for Oncology Drug Use and Drug Compendia: History and Current Status, 1 J. ONCOLOGY PRAC. 102, 104 (2005); James M. Beck & Elizabeth D. Azari, *FDA, Off-Label Uses, and*

One FDA regulation even expressly permits ‘scientific exchange’ about unapproved uses of investigational drug products.¹⁰ Nevertheless, because the precise contours of scientific exchange are unclear,¹¹ FDA’s regulatory framework significantly restricts manufacturers from sharing information about their products that deviates, in any way, from the FDA-approved label. The consequences for manufacturers who engage in off-label promotion can be severe: the government can seek criminal penalties under the FDCA¹² (and may exclude manufacturers from participation in Medicare and Medicaid in the event of a criminal conviction¹³), and acts of off-label promotion may also serve as the basis for qui tam lawsuits under the False Claims Act (‘FCA’).¹⁴

The current regulatory framework appears outdated and does not fit with the modern communications and promotional landscape in which manufacturers seek to communicate with a host of players, including healthcare professionals, payors, formulary committees, and consumers, among others, by a range of traditional and contemporary media. Not all manufacturer communications are intended to propose an immediate commercial transaction for a drug; indeed, many modern communications by manufacturers are more educational than promotional and are intended to provide healthcare professionals with the most accurate, up-to-date medical information to inform their medical decision-making. FDA’s current regulatory framework overly limits access to information about new uses of previously approved drugs by significantly restricting manufacturers’ communications about their products. The current regulatory and enforcement approach come at the expense of fostering innovation and enhancing access to up-to-date information about therapeutic agents, and it also conflicts with manufacturers’ First Amendment rights under the Constitution.

Accordingly, we propose a new regulatory framework (the ‘New Model’) which attempts to restore the balance between information access and patient safety, while also aligning FDA’s regulatory approach with the FDCA and the Constitution. The New Model we propose would create three categories of manufacturer communications—(1) Scientific Exchange and Other Exempt Communications, (2) Non-Core Communications, and (3) Core Communications—that would be regulated consistent with the First Amendment and according to the strength of the government’s interest in regulating the specific communications included within each category. The New Model

Informed Consent: Debunking Myths and Misconceptions, 53 FOOD & DRUG L.J. 71, 80 n.76, 85 (1998); Briana R. Barron, *Silent Warning: The FDA’s Ban On Off-Label Speech: Is It Protecting Our Safety?*, 94 MARQ. L. REV. 983, 988–89 (2011); Randall S. Stafford, *Regulating Off-Label Drug Use — Rethinking the Role of the FDA*, 358 NEW ENG. J. MED. 1427, 1427 (2008).

¹⁰ 21 C.F.R. § 312.7(a).

¹¹ Indeed, the Medical Information Working Group (‘MIWG’), a consortium of several pharmaceutical and medical device companies, submitted two citizen petitions to FDA in recent years requesting that the agency clarify its policies related to scientific exchange. See *Citizen Petition from MIWG*, Docket No. FDA-2013-P-1079, Sept. 3, 2013, <http://www.regulations.gov/#!documentDetail;D=FDA-2013-P-1079-0001> (accessed Apr. 10, 2015); *Citizen Petition from MIWG*, Docket No. FDA-2011-P-0512, July 5, 2011, <http://www.regulations.gov/#!documentDetail;D=FDA-2011-P-0512-0001> (accessed Apr. 10, 2015). FDA has even solicited public comments regarding scientific exchange. 76 Fed. Reg. 81508 (Dec. 28, 2011).

¹² See 21 U.S.C. § 333.

¹³ See 42 U.S.C. § 1320a-7.

¹⁴ See 31 U.S.C. § 3729. In the off-label promotion context, the typical qui tam suit under the FCA will allege that a pharmaceutical company promoted an off-label use of a drug and caused the filing of a fraudulent claim for reimbursement from Medicare or Medicaid.

should address the FDA's concerns related to off-label speech while protecting manufacturers' freedom to engage in truthful and non-misleading communications about their products.

Part II of this article describes the commercial speech doctrine and First Amendment case law relevant to assessing FDA's regulatory framework. Part III provides an overview of FDA's current regulatory framework. Part IV discusses the need for a new regulatory framework and describes what the objectives and underpinnings of any New Model should be. Finally, part V describes the New Model in detail by defining each category of communications, providing representative examples, and justifying the level of proposed authority provided to FDA for each category.

II. FIRST AMENDMENT PROTECTION OF DRUG MANUFACTURER SPEECH

One of the most familiar, fundamental constitutional rights is the First Amendment right to freedom of speech. Supreme Court jurisprudence analyzing laws and regulations that restrict freedom of speech has established that different categories of speech are afforded with different levels of protection. Today, pharmaceutical manufacturer speech is generally considered 'commercial speech' for the purposes of this analysis.¹⁵ However, FDA's regulatory framework, as described in part III, *infra*, was originally developed at a time when the First Amendment rights of pharmaceutical manufacturers were less concrete. Indeed, until 1976, the Supreme Court did not even recognize 'commercial speech' as a form of protected speech.¹⁶ In *Virginia State Board of Pharmacy v. Virginia Citizens Consumer Council, Inc.* in 1976, the Supreme Court held that commercial speech—speech that may do 'no more than propose a commercial transaction'—still enjoys constitutional protection.¹⁷

As discussed in this part, subsequent cases have expounded upon the definition of commercial speech and the level of scrutiny that applies to commercial speech, both generally and in the context of several cases that have examined FDA's regulatory framework. More recent caselaw—*Sorrell v. IMS Health Inc.*¹⁸ and *United States v. Caronia*¹⁹—has even indicated that content- and speaker-based restrictions on drug manufacturer speech are subject to 'heightened scrutiny' under the First Amendment. Additionally, recent caselaw addressing 'fair notice' requirements under the due process clause of the Fifth Amendment is highly relevant to this First Amendment analysis.

¹⁵ E.g., Joseph Leghorn, Elizabeth Brophy & Peter Rother, *The First Amendment and FDA Restrictions on Off-Label Uses: The Call for a New Approach*, 63 FOOD & DRUG L.J. 391, 400 (2008) ('[T]he few cases which have addressed whether FDA can restrict off-label speech have concluded that off-label promotion is commercial speech.') (citing *Thompson v. W. States Med. Ctr.*, 535 U.S. 357, 366 (2002); *United States v. Caputo*, 288 F. Supp. 2d 912, 920 (N.D. Ill. 2003)).

¹⁶ See Thomas Jackson & John Jeffries, Jr., *Commercial Speech: Economic Due Process and the First Amendment*, 65 VA. L. REV. 1, 1 (1979) (noting that 'the Supreme Court refused to apply the first amendment to 'commercial speech' prior to 1976 (citing *Breard v. City of Alexandria*, 341 U.S. 622 (1951); *Valentine v. Chrestensen*, 316 U.S. 52 (1942); *Pittsburgh Press Co. v. Pittsburgh Comm'n on Human Relations*, 413 U.S. 376, 385 (1973))).

¹⁷ *Virginia State Bd. of Pharmacy v. Virginia Citizens Consumer Council, Inc.*, 425 U.S. 748, 758–60 (1976) (holding that a state law barring pharmacists' from advertising prescription drug prices was unconstitutional).

¹⁸ 131 S. Ct. 2653 (2011).

¹⁹ 703 F.3d 149 (2d Cir. 2012).

II.A Early Case Law: Defining Commercial Speech and Applying the First Amendment to Regulated Industry

In the years following *Virginia State Board of Pharmacy*, the Supreme Court established both a framework for analyzing restrictions on commercial speech and for distinguishing between commercial and non-commercial speech, but FDA, relying on a court of appeals decision²⁰ suggesting that this commercial speech analysis was not directly applicable in highly regulated industries, attempted to sidestep First Amendment concerns regarding its regulatory framework.

Commercial speech in its purest form is ‘expression related solely to the economic interests of the speaker’²¹ and ‘speech which does no more than propose a commercial transaction’.²² In *Bolger v. Youngs Drug Products Corp.*, the Court set forth three factors that, when taken together, strongly supported the classification of the materials at issue in the case as commercial speech: (1) the speech is meant to be an advertisement, (2) the speech references a particular product, and (3) there is an economic motivation for disseminating the material.²³ To a certain extent, this three-factor test calls into question the regulation of certain drug manufacturer speech as commercial speech, given that some manufacturer communications are intended for educational or scientific purposes, rather than as advertisements proposing a commercial transaction.

The Supreme Court has emphasized that commercial speech still deserves constitutional protection, albeit a ‘lesser protection’ than other categories of constitutionally protected speech.²⁴ ‘With respect to non-commercial speech’, the Court has ‘sustained content-based restrictions only in the most extraordinary circumstances’.²⁵ For commercial speech, on the other hand, the Court has noted that content-based restrictions ‘may be permissible’ due to ‘the greater potential for deception or confusion in the context of certain advertising messages’.²⁶ In *Central Hudson Gas & Electric Corp. v. Public Service Commission*, the Court established a four-part test for assessing the constitutionality of a restriction on commercial speech: (1) whether the speech at issue concerns lawful activity and is not misleading; (2) whether the asserted government interest is substantial; (3) if so, whether the regulation directly advances the governmental interest asserted; and (4) whether it is not more extensive than is necessary to serve that interest.²⁷ Because drug manufacturer speech is generally considered commercial speech, courts have typically applied the *Central Hudson* test, a form of ‘intermediate scrutiny’,²⁸ when analyzing restrictions on such speech.²⁹

²⁰ See *SEC v. Wall Street Publishing Institute, Inc.*, 851 F.2d 365 (D.C. Cir. 1988).

²¹ *Central Hudson Gas & Elec. Corp. v. Public Serv. Comm’n*, 447 U.S. 557, 561–63 (1980).

²² *Bolger v. Youngs Drug Prods. Corp.*, 463 U.S. 60, 66 (1983).

²³ *Id.* at 66, 67 (‘The combination of all these characteristics ... provides strong support for the ... conclusion that the informational pamphlets are properly characterized as commercial speech.’).

²⁴ *Central Hudson*, 447 U.S. at 561, 563 (‘[O]ur decisions have recognized ‘the commonsense distinction between speech proposing a commercial transaction, which occurs in an area traditionally subject to government regulation, and other varieties of speech.’ (citing *Ohralik v. Ohio State Bar Ass’n*, 436 U.S. 447, 455–56 (1978)).

²⁵ *Bolger*, 463 U.S. at 65.

²⁶ *Id.*

²⁷ See *Central Hudson*, 447 U.S. at 566.

²⁸ *Id.* at 573 (Blackmun, J., concurring in the judgment).

²⁹ See Part II.B–C, *infra*.

Despite the broad holding in *Central Hudson* applicable to all forms of commercial speech, the D.C. Circuit's 1988 decision in *SEC v. Wall Street Publishing Institute, Inc.* rejected the application of *Central Hudson* test in the context of securities regulation.³⁰ The court concluded that the *Central Hudson* test was not applicable,³¹ explaining: 'In areas of extensive federal regulation—like securities dealing—we do not believe the Constitution requires the judiciary to weigh the relative merits of particular regulatory objectives that impinge upon communications occurring within the umbrella of an overall regulatory scheme'.³²

FDA viewed the rationale of *Wall Street Publishing* as equally applicable to the Agency's regulatory framework for drugs and medical devices. When issuing a 1997 guidance document addressing industry supported continuing medical education activities ('CME Guidance'), FDA relied on *Wall Street Publishing* for the proposition that in heavily regulated industries, the government has great authority to restrict speech that would otherwise be protected under the First Amendment.³³ The Agency concluded: 'In view of the fact that the regulation of drugs and devices is an area of extensive federal regulation, the agency may regulate the communications at industry-supported scientific and educational activities without violating the First Amendment'.³⁴ FDA has not expressly cited *Wall Street Publishing* in recent years to justify its restrictions on off-label speech likely because the relevance of *Wall Street Publishing* to FDA's regulatory framework was rejected in subsequent litigation.³⁵ Nonetheless, the Agency's actions are generally still consistent with the position expressed in 1997 supporting the applicability of *Wall Street Publishing* to FDA's regulatory framework.

II.B Setting the Stage: Judicial Skepticism of FDA's Regulatory Framework

Caselaw subsequent to *Wall Street Publishing*—notably litigation brought by the Washington Legal Foundation ('WLF') against FDA—has highlighted growing judicial skepticism regarding the constitutionality of FDA's regulatory framework as applied to manufacturer speech. In the 1990s and early 2000s, several courts addressing First Amendment challenges to FDA's regulatory framework found that various restrictions on speech by FDA failed the *Central Hudson* test.³⁶

In a First Amendment challenge brought by the WLF to three FDA guidance documents³⁷ that touched on off-label speech by addressing the dissemination of journal articles and reference texts and industry-supported continuing medical education (and

³⁰ See *SEC v. Wall Street Publishing Institute, Inc.*, 851 F.2d 365 (D.C. Cir. 1988).

³¹ See *id.* at 373 (finding that it was not necessary 'to inquire, as we would if only commercial speech were involved, whether the government's specific regulatory objective—disclosure of consideration—is constitutionally permissible').

³² *Id.*

³³ See 62 Fed. Reg. 64073, 64077 (Dec. 3, 1997). FDA described *Wall Street Publishing* as 'most analogous to FDA's regulation of industry-supported scientific and educational activities'. *Id.*

³⁴ *Id.* at 64077, 64078.

³⁵ See *infra* text accompanying note 39.

³⁶ See *Thompson v. W. States Med. Ctr.*, 535 U.S. 357 (2002); *Pearson v. Shalala*, 164 F.3d 650, 653 (D.C. Cir. 1999) ('*Pearson I*'); *Pearson v. Shalala*, 130 F. Supp. 2d 105, 111 (D.C. Cir. 2001) ('*Pearson II*'); *WLF v. Friedman*, 13 F. Supp. 2d 51 (D.D.C. 1998) ('*WLF I*'), amended by 36 F. Supp. 2d 16 (D.D.C. 1999) ('*WLF II*'), amended by *WLF v. Henney*, 56 F. Supp. 2d 81 (D.D.C. 1999) ('*WLF III*'), vacated as moot by *WLF v. Henney*, 202 F.3d 331 (D.C. Cir. 2000) ('*WLF IV*').

³⁷ See *CME Guidance*, 62 Fed. Reg. 64074, 64093 (Dec. 3, 1997); *Guidance to Industry on Dissemination of Reprints of Certain Published, Original Data*, 61 Fed. Reg. 52800, 52801 (Oct. 8, 1996) ('1996 Reprint

the statutory provisions that subsequently superseded the guidance documents relating to journal articles and reference texts³⁸), the district court rejected FDA's argument based on *Wall Street Publishing* that restrictions on speech should receive only limited First Amendment scrutiny.³⁹ Applying *Central Hudson*, the court concluded that off-label speech is not inherently misleading merely by virtue of addressing an unapproved use,⁴⁰ nor is off-label speech directed toward unlawful activities because off-label *prescribing* is perfectly legal.⁴¹ The court held that the restrictions on off-label speech, although they advanced a 'substantial government interest', were 'more extensive than necessary to serve' this interest, thereby failing the *Central Hudson* test and violating the First Amendment.⁴² However, upon appeal, the D.C. Circuit treated the case as moot because FDA stipulated that the relevant statutory provisions in FDAMA did not provide any independent authority for enforcement but merely operated as a 'safe harbor'.⁴³ Hence, the WLF's victory against FDA was completely vacated, and the FDA managed to avoid what would have been a significant blow to the Agency's ability to prohibit off-label promotion.⁴⁴ Nonetheless, the WLF line of cases is still instructive for how a court would assess the FDA's regulatory framework today.

Other cases have also emphasized the government's difficult burden in satisfying the fourth prong of the *Central Hudson* test: that a restriction on speech be no more extensive than necessary to serve the government's interest. In *Thompson v. Western States Medical Center*, the Supreme Court's only decision addressing a First Amendment challenge to FDA regulation—albeit in the context of pharmacy compounding, rather than the context of traditionally manufactured drugs, the Court emphasized '[I]f the Government could achieve its interests in a manner that does not restrict speech, or that restricts less speech, the Government *must do so*'.⁴⁵ This principle makes clear

Guidance'); Guidance for Industry Funded Dissemination of Reference Texts, 61 Fed. Reg. 52800, 52801 (Oct. 8, 1996) ('1996 Textbook Guidance').

³⁸ Certain provisions of the Food and Drug Administration Modernization Act ('FDAMA') of 1997, Pub L. No. 105-115, § 401, 111 Stat. 2296 (1997), related to the dissemination of reprints and textbooks took effect that superseded the 1996 Reprint Guidance and the 1996 Textbook Guidance.

³⁹ See WLF I, 13 F. Supp. 2d at 60.

⁴⁰ See *id.* at 68.

⁴¹ See *id.* at 65, 69.

⁴² *Id.* at 74. Subsequently, after the FDAMA provisions took effect, the district court clarified that the order issued in WLF I applied to FDA's underlying policies and not just the guidance documents themselves, which FDAMA had superseded. WLF II, 36 F. Supp. 2d 16, 18 (D.D.C. 1999) ('WLF II'). The district court found, for many of the same reasons described in WLF I, that the FDAMA provisions and FDA's implementing regulations violated the First Amendment. See WLF III, 56 F. Supp. 2d 81, 82 (D.D.C. 1999), vacated as moot by WLF IV, 202 F.3d 331 (D.C. Cir. 2000).

⁴³ WLF IV, 202 F.3d at 334, 335 ('The government agreed ... that the agency would draw no independent prosecutorial authority from FDAMA to buttress any enforcement proceeding' and 'insists that nothing in either of the provisions challenged in this case provides the FDA with independent authority to regulate manufacturer speech.'). Interestingly, despite the FDA's position before the D.C. Circuit, the agency had issued at least one warning letter after the passage of FDAMA to a drug manufacturer that allegedly engaged in off-label promotion by disseminating certain reprint articles. See Warning Letter to Duane Burnham, Abbott Labs., from Minnie Baylor-Henry, FDA (June 26, 1998), <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/EnforcementActivitiesbyFDA/WarningLettersandNoticeofViolationLetterstoPharmaceuticalCompanies/UCM168187.pdf> (accessed Apr. 10, 2015).

⁴⁴ WLF v. Henney, 128 F. Supp. 2d 11, 15 (D.D.C. 2000) ('WLF V').

⁴⁵ *Thompson v. W. States Med. Ctr.*, 535 U.S. 357, 371 (2002) (holding the FDCA's prohibition on advertising and promotion of compounded drugs by pharmacies to be unconstitutional). The Court then provided

that any restriction on drug manufacturer speech will fail the fourth prong of the *Central Hudson* test, unless there are no less restrictive alternatives that could achieve the same objectives. One such less restrictive alternative to an outright prohibition on particular speech is to permit the speech, provided it is accompanied by an appropriate disclaimer.⁴⁶ In other words, a disclaimer can mitigate or cure the potentially misleading nature of a claim. Put another way by one legal commentator:

Western States leaves outright prohibitions designed to dampen demand (or to serve other collateral purposes) vulnerable to constitutional invalidation, while more limited restrictions or disclosure requirements designed to guard against potentially misleading promotional messages would seem to survive.⁴⁷

II.C Recent Judicial Developments: First Amendment Protection and Due Process Considerations for Drug Manufacturer Speech

Two recent cases—*Sorrell v. IMS Health Inc.*⁴⁸ and *United States v. Caronia*⁴⁹—have applied heightened First Amendment scrutiny to restrictions on drug manufacturer speech. Additionally, the Supreme Court’s recent decision in *FCC v. Fox Television Stations, Inc.* (‘Fox II’)⁵⁰ under the due process clause of the Fifth Amendment indicates that ‘fair notice’ considerations are highly relevant in the context of First Amendment challenges.

II.C.1 *Sorrell v. IMS Health, Inc.* (2011)

A decade after the *WLF* litigation, the Supreme Court weighed in on the government’s ability to restrict speech related to the marketing of prescription drugs. The state law being challenged in *Sorrell* severely restricted the ability of pharmacies to disclose, and the ability of pharmaceutical manufacturers to use, prescriber-identifying information for marketing purposes.⁵¹ The Court applied ‘heightened scrutiny’ to the state law because it impermissibly created both speaker-based and content-based restrictions on speech.⁵² The Court concluded that it was facially ‘speaker-based’ because it ‘disfavor[ed] specific speakers, namely pharmaceutical manufacturers’, and facially

examples of several ‘non-speech-related means’ by which the Government could have served its asserted interests in distinguishing between compounding and large-scale drug manufacturing and protecting the FDA’s new drug approval process. *Id.* at 372.

⁴⁶ See *Pearson I*, 164 F.3d 650, 655–59 (D.C. Cir. 1999) (holding that FDA’s restrictions on the ability of dietary supplement firms to make health claims not supported by ‘significant scientific agreement’ were more extensive than necessary because FDA refused to permit firms to use appropriate disclaimers to qualify claims); *Pearson II*, 130 F. Supp. 2d 105, 118–21 (D.D.C. 2001) (holding that health claims not supported by ‘significant scientific agreement’ were still subject to First Amendment protection and that FDA had not made requisite showing that disclaimer’s could not cure a claim’s alleged misleadingness).

⁴⁷ Lars Noah, *Truth or Consequences?: Commercial Free Speech v. Public Health Promotion (At the FDA)*, 21 HEALTH MATRIX 31, 67 (2011).

⁴⁸ *Sorrell v. IMS Health Inc.*, 131 S. Ct. 2653 (2011).

⁴⁹ *United States v. Caronia*, 703 F.3d 149 (2d Cir. 2012).

⁵⁰ *FCC v. Fox Television Stations, Inc.*, 132 S. Ct. 2307 (2012).

⁵¹ *Sorrell*, 131 S. Ct. at 2660.

⁵² See *id.* at 2666 (stating that ‘Vermont’s law imposes a content- and speaker-based burden on respondents’ own speech’ and ‘[t]hat consideration . . . requires heightened judicial scrutiny’).

‘content-based’ because it ‘disfavor[ed] marketing’.⁵³ The Court’s heightened scrutiny analysis assessed whether the law ‘directly advance[d] a substantial government interest’ and was ‘drawn to achieve that interest’.⁵⁴ Without definitively classifying the speech as ‘commercial’,⁵⁵ the Court concluded that the law could not withstand heightened scrutiny because it did not advance the asserted state interests ‘in a permissible way’.⁵⁶

For example, the state’s asserted interest in preventing detailers (i.e., sales representatives) from ‘influenc[ing] treatment decisions’ was ‘contrary to basic First Amendment principles’,⁵⁷ since a ‘fear that speech might persuade provides no lawful basis for quieting it’.⁵⁸ The Court further cautioned that speech restrictions ‘seek[ing] to keep people in the dark for what the government perceives to be their own good’ are especially suspect,⁵⁹ and emphasized the importance of the ‘free flow of commercial speech’ in the ‘fields of medicine and public health’.⁶⁰

II.C.2 United States v. Caronia (2012)

The following year, the Second Circuit in *Caronia* applied the *Sorrell* ‘heightened scrutiny’ analysis to a First Amendment challenge by Alfred Caronia, a pharmaceutical sales representative who had been criminally prosecuted under the FDCA based on his alleged off-label promotion of a drug.⁶¹ Caronia argued that the First Amendment does not permit the government to restrict a pharmaceutical manufacturer’s truthful and non-misleading speech involving off-label promotion when other actors do not face the same restrictions.⁶² The Second Circuit agreed and vacated Caronia’s conviction.⁶³

The court rejected the government’s argument that Caronia was not actually prosecuted for his speech and that the First Amendment therefore did not apply. However, the court relied on numerous statements in the trial transcript to demonstrate that ‘the government’s theory of prosecution identified Caronia’s speech alone as the proscribed

⁵³ *Id.* at 2663 (highlighting that ‘the information may be purchased or acquired by other speakers with diverse purposes and viewpoints’).

⁵⁴ *Id.* at 2667–68.

⁵⁵ The court did not explicitly label the speech as ‘commercial speech’, noting instead that the ‘the outcome [would be] the same whether a special commercial speech inquiry [presumably referring to *Central Hudson*] or a stricter form of judicial scrutiny is applied’ and that there was therefore ‘no need to determine whether all speech hampered by [the Vermont statute] is commercial, as our cases have used that term’. *Id.* at 2667.

⁵⁶ *Id.* at 2670. Because the law only applied to a ‘narrow class of disfavored speakers’, the Court found that the asserted state interest of preserving physician confidentiality ‘d[id] not justify the burden [the law] places on protected expression’. *Id.* at 2668. The state also asserted an interest in ‘protect[ing] doctors’ from the harassment of pharmaceutical sales representatives, but, according to the Court, ‘offer[ed] no explanation why remedies other than content-based rules would be inadequate’. *Id.* at 2669.

⁵⁷ *Id.* at 2670.

⁵⁸ *Id.* (quoting *Brandenburg v. Ohio*, 395 U.S. 444, 447 (1969) (per curiam)).

⁵⁹ *Id.* at 2671.

⁶⁰ *Id.* at 2664 (internal quotations omitted).

⁶¹ *United States v. Caronia*, 703 F.3d 149, 152 (2d Cir. 2012). The charges against Caronia were based on two taped meetings in which Caronia ‘plainly promoted the use of Xyrem in unapproved indications’ to a government informant posing as a customer. *Id.* at 156.

⁶² See *id.* at 160. Caronia contended that because the regulatory scheme permits physicians to prescribe drugs for off-label uses and allows other individuals (i.e., those not acting on behalf of a manufacturer) to discuss freely and even recommend off-label uses, the government could not criminalize his speech without running afoul of the First Amendment.

⁶³ *Id.* at 152.

conduct'.⁶⁴ The government clearly did not treat his speech as mere 'evidence of intent'.⁶⁵

The court evaluated Caronia's conviction under the 'heightened scrutiny' standard set forth in *Sorrell*: content-based and speaker-based speech restrictions are 'subject to heightened scrutiny and... "presumptively invalid"'.⁶⁶ Just as in *Sorrell*, the Caronia court determined that the FDCA, as applied by the government, would fail both heightened scrutiny and intermediate scrutiny under the *Central Hudson* test.⁶⁷ In addition, the court recognized that criminal restrictions on speech must be 'scrutinized with particular care'.⁶⁸

Notably, the court did not hold FDCA's misbranding provisions unconstitutional. Applying the 'constitutional avoidance canon',⁶⁹ the court interpreted the FDCA to not prohibit manufacturer 'speech promoting the lawful, off-label use of an FDA-approved drug', because under a contrary interpretation, the FDCA would violate the First Amendment.⁷⁰

Although both *Sorrell* and *Caronia* seem to extend greater protection to off-label manufacturer speech, the exact scope of their holdings is not completely clear. First, *Sorrell* concluded that 'heightened scrutiny' should apply in cases of speaker- and content-based restrictions on speech, but the Court did not define the 'heightened scrutiny' standard.⁷¹ As both cases held that the challenged restrictions failed both intermediate

⁶⁴ See *id.* at 161 (stating that 'government clearly prosecuted Caronia for his words' and that both the jury instructions and government's summation indicated that 'Caronia's speech was itself the proscribed conduct').

⁶⁵ Because the court ultimately rested its conclusion that Caronia was prosecuted solely for his speech based on the trial transcript, it did not clarify whether the government could ever succeed on an 'evidence of intent' argument. See *id.* at 161 (noting that '[t]he government never argued in summation or rebuttal that the promotion was evidence of intent' and that 'the record makes clear that the government prosecuted Caronia for his promotion and marketing efforts'). However, the opinion suggests that the government would not have succeeded in this argument, even if it were less clear in the transcript that speech was the proscribed conduct. See *id.* at 168 ('[E]ven if speech can be used as evidence of a drug's intended use, we decline to adopt the government's construction of the FDCA's misbranding provisions to prohibit manufacturer promotion alone as it would unconstitutionally restrict free speech.').

⁶⁶ *Id.* at 164, 165 ('The government's construction of the FDCA's misbranding provisions to prohibit and criminalize the promotion of off-label drug use by pharmaceutical manufacturers is content- and speaker-based, and, therefore, subject to heightened scrutiny.').

⁶⁷ See *id.* at 164, 166–67. But see 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, 359 (2013) (wondering whether the Caronia court's application of the *Central Hudson* test was 'intermediate scrutiny in name only').

⁶⁸ Caronia, 703 F.3d at 163 (quoting *City of Houston v. Hill*, 482 U.S. 451, 459, (1987)); see also *id.* at 165 ('Additionally, a claim to First Amendment protection here is more compelling than in *Sorrell* because this case involves a criminal regulatory scheme subject to more careful scrutiny.').

⁶⁹ Under this 'canon of construction', when a given interpretation of a law raises a 'serious constitutional question', the reviewing court would interpret the statute in another way to avoid raising the constitutional concern. See *id.* at 162 (citing *Skilling v. United States*, 130 S. Ct. 2896, 2929–30 (2010)).

⁷⁰ The court explicitly stated that the 'government's construction of the FDCA's misbranding provisions to prohibit manufacturer promotion alone ... would unconstitutionally restrict free speech'. *Id.* at 168. As one circuit court of appeals has stated regarding science-based communications more generally: '[T]o the extent a speaker or author draws conclusions from non-fraudulent data, based on accurate descriptions of the data and methodology underlying those conclusions, on subjects about which there is legitimate ongoing scientific disagreement, those statements are not grounds' for proscribing the statements as false or misleading. *Ony, Inc. v. Cornerstone Therapeutics, Inc.*, 720 F.3d 490, 498 (2d Cir. 2013).

⁷¹ See Caronia, 703 F.3d at 164 (noting that *Sorrell* 'did not decide the level of heightened scrutiny to be applied, that is, strict, intermediate, or some other form of heightened scrutiny').

and heightened scrutiny, courts are left with little guidance on how to resolve a case if a restriction fails heightened scrutiny but passes intermediate scrutiny.⁷² Second, while *Caronia* clearly holds that the FDCA does not authorize the government to prosecute ‘manufacturer promotion alone’,⁷³ it may be unclear how *Caronia* applies to cases of off-label promotion that involve additional activities beyond pure speech. Going forward, the government may focus its enforcement efforts on false and misleading aspects of off-label speech.⁷⁴

I.I.C.3 *FCC v. Fox Television Stations, Inc. (‘Fox II’) (2012)*

The same year *Caronia* was decided, the Supreme Court handed down another highly relevant speech case, in which it applied not the First Amendment but the Fifth.⁷⁵ In *Fox II*, the Federal Communication Commission (‘FCC’) brought an enforcement action against two television networks for broadcasting ‘obscene, indecent, or profane language’ in violation of federal law. Without addressing the First Amendment question,⁷⁶ the Supreme Court held that the FCC violated the due process clause of the Fifth Amendment for failing to give the broadcasters ‘fair notice’ that such broadcasts were ‘actionably indecent’.⁷⁷ Thus, the FCC’s standards as applied in *Fox II* were unconstitutionally vague.⁷⁸ The Court recognized that adherence to fair notice requirements is especially critical when speech regulations are involved so as ‘to ensure that ambiguity does not chill protected speech’.⁷⁹ This holding is highly relevant to FDA’s regulation of off-label speech by drug manufacturers because FDA’s regulatory framework is marked by a significant lack of clarity.⁸⁰

In brief, the cases described in this part establish (or at least, with respect to the Second Circuit’s *Caronia* decision, strongly support) four fundamental principles.

1. The First Amendment does not allow the government to prosecute truthful and non-misleading off-label speech by drug manufacturers under the FDCA.

⁷² See Marc J. Scheineson & Guillermo Cuevas, *United States v. Caronia: The Increasing Strength of Commercial Free Speech and Potential New Emphasis on Classifying Off-Label Promotion as ‘False And Misleading’*, 68 *FOOD & DRUG L.J.* 201, 210 (2013) (noting that the court in *Caronia* ‘also engaged in a *Central Hudson* analysis ... probably due to the fact that *Sorrell* failed to articulate a specific standard of review’).

⁷³ *Caronia*, 703 F.3d at 168; See 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, 1573–74 (2014) (acknowledging that the *Caronia* court’s analysis ‘raises the question of what avenues remain for government regulation of ... pharmaceutical manufacturers’ off-label promotional speech’).

⁷⁴ See Scheineson & Cuevas, *supra* note 72, at 211, 216.

⁷⁵ *FCC v. Fox Television Stations, Inc.*, 132 S. Ct. 2307 (2012).

⁷⁶ See *id.* at 2320 (‘Court resolves these cases on fair notice grounds under the Due Process Clause, it need not address the First Amendment implications of the Commission’s indecency policy.’).

⁷⁷ See *id.* at 2320.

⁷⁸ *Id.*

⁷⁹ *Id.* at 2317.

⁸⁰ See Part III.D, *infra*; *Letter from MIWG to FDA, Docket Nos. FDA-2011-P-0512 and FDA-2011-D-0868*, Mar. 1, 2013 (noting that ‘*Fox II* points up the importance of Due Process principles in FDA’s regulation of manufacturer speech about off-label uses’ because ‘the current regulatory framework is not sufficiently clear’ and because of its failure to ‘provide fair notice of [its] interpretations of key statutory provisions prior to commencing regulatory action based on them.’), <http://www.regulations.gov/#!documentDetail;D=FDA-2011-P-0512-0008> (accessed Apr. 10, 2015).

2. Restrictions on drug manufacturer speech that are content-based and speaker-based are presumptively unconstitutional.
3. Broad, categorical bans on speech are unconstitutional unless no less restrictive alternatives would achieve the same objectives.
4. Restrictions on speech must be sufficiently clear to provide fair notice to regulated parties of what is required of them.

III. FDA'S CURRENT REGULATORY FRAMEWORK

The FDCA gives FDA the authority to regulate the labeling and advertising of drugs.⁸¹ A complex system of provisions in the FDCA and FDA regulations—derived from FDA's authority over labeling and advertising and the regulatory definition of 'intended use'—create an implicit, yet well-known prohibition of off-label promotion. Other FDA regulations further limit and sometimes effectively prohibit even on-label communications by manufacturers by requiring such communications to generally be supported by 'substantial evidence'.⁸² Notably, the FDCA and FDA's implementing regulations do not in any way restrict communications about a drug among physicians, scientists, and other healthcare professionals not affiliated with the pharmaceutical company. FDA only regulates speech by drug companies and their agents. We contend that FDA's regulatory approach to off-label promotion, and lack of clarity regarding what manufacturer communications addressing off-label uses may be permitted, results in a chilling effect: to avoid the risk of a criminal prosecution or qui tam lawsuit under the FDCA, many drug manufacturers choose to refrain from even truthful and non-misleading communications if they could be construed by the government as off-label promotion.

This part first describes FDA's current regulatory framework, including the Agency's authority over labeling, the intended use regulation, and the substantial evidence requirement. It concludes by discussing recent Agency efforts—in the form of one-off guidance documents on various specific issues—that have attempted, but largely failed, to provide drug manufacturers with some leeway to make certain communications that the Agency would otherwise consider off-label or lacking in substantial evidence.

III.A FDA's Authority over Labeling and Advertising

The FDCA affords FDA broad authority to regulate labeling,⁸³ with only narrow authority over prescription drug advertising and no specific authority over over-the-counter drug advertising.⁸⁴ The FDCA defines a 'label' as 'a display of written, printed, or graphic matter upon the immediate container of any article'.⁸⁵ 'Labeling' is defined as 'all labels and other written, printed, or graphic matter (1) upon any article or any of its containers or wrappers or (2) accompanying such article at any time while a device

⁸¹ See, e.g., 21 U.S.C. § 352(a), (n).

⁸² See 21 C.F.R. §§ 201.57(c)(2)(iii)-(v); 202.1(e)(6).

⁸³ See, e.g., 21 U.S.C. § 352(a) (deeming a drug or device misbranded if its labeling is false or misleading in any particular).

⁸⁴ See FTC-FDA Memorandum of Understanding, 36 Fed. Reg. 18539 (Sept. 16, 1971). The FDCA requires that prescription drug advertisements contain a true statement of the established name of the drug, the drug formula, and a brief summary of side effects, contraindications, and effectiveness for the drug. See 21 U.S.C. § 352(n).

⁸⁵ 21 U.S.C. § 321(k).

is held for sale after shipment or delivery for shipment in interstate commerce'.⁸⁶ The FDCA does not define 'advertising', although FDA regulations suggest that the term refers to forms of manufacturer speech that are 'published' or 'broadcast' in third-party media.⁸⁷

In a landmark decision in *Kordel v. United States* in 1948, the Supreme Court held that the term 'accompanying such article' does not restrict the definition of labeling to materials that physically accompany the article.⁸⁸ Instead, the Court stated: 'One article or thing is accompanied by another when it supplements or explains it, in the manner that a committee report of the Congress accompanies a bill. No physical attachment one to the other is necessary. It is the *textual relationship* that is significant'.⁸⁹ Under this analysis, the Court concluded that materials shipped separately from a product can constitute 'labeling' when they 'perform the function of labeling' even if they are not physically shipped with the product.⁹⁰ The Court, however, did not hold that any material or document related to the drug constitutes labeling.⁹¹ It emphasized that the materials at issue were part of an 'integrated distribution program' and 'interdependent', serving as an 'essential supplement' to the package label.⁹² The Court specifically noted that the literature at issue 'explained the[] uses' of the drugs and that '[n]owhere else was the purchaser advised how to use them.'⁹³ One issue that was not made entirely clear by the Court's decision was whether materials, even if shipped separately from the product, could constitute labeling if they do not come together with the product at some point after shipment in interstate commerce.⁹⁴

In the decades since *Kordel*, FDA has taken the position that physical proximity to a product does not matter when determining whether materials are labeling and takes an expansive view of the materials that qualify as labeling.⁹⁵ Today, FDA generally recognizes two types of labeling: (1) FDA-required labeling and (2) promotional labeling.⁹⁶ FDA-required labeling, (i.e., labeling on or within the package from which

⁸⁶ 21 U.S.C. § 321(m).

⁸⁷ 21 C.F.R. § 202.1(l)(1) ('Advertisements ... include advertisements in published journals, magazines, other periodicals, and newspapers, and advertisements broadcast through media such as radio, television, and telephone communication systems.').

⁸⁸ *Kordel v. United States*, 335 U.S. 345, 350 (1948).

⁸⁹ *Id.* at 350 (emphasis added).

⁹⁰ *Id.* at 351.

⁹¹ See *id.* at 349,351.

⁹² *Id.* at 348, 350.

⁹³ *Id.* at 348.

⁹⁴ See Coleman, *supra* note 4, at 184, 188. Less than a decade after *Kordel*, one circuit court of appeals held that only the functional purpose of materials matters in determining whether they qualify as labeling and did not consider whether the materials ever came together with the product in interstate commerce. See V.E. Irons, Inc. v. United States, 244 F.2d 34, 39 (1st Cir. 1957) (holding that sales kits and brochures intended to educate the company's distributors and instruct them how to sell the company's product constituted labeling).

⁹⁵ See, e.g., 21 C.F.R. § 202.1(l)(2) ('Brochures, booklets, mailing pieces, detailing pieces, file cards, bulletins, calendars, price lists, catalogs, house organs, letters, motion picture films, film strips, lantern slides, sound recordings, exhibits, literature, and reprints and similar pieces of printed, audio, or visual matter descriptive of a drug and references published (for example, the "Physicians Desk Reference") for use by medical practitioners, pharmacists, or nurses, containing drug information supplied by the manufacturer, packer, or distributor of the drug and which are disseminated by or on behalf of its manufacturer, packer, or distributor are hereby determined to be labeling as defined in section 201(m) of the act'.).

⁹⁶ See, e.g., FDA, *Draft Guidance for Industry: Internet/Social Media Platforms with Character Space Limitations—Presenting Risk and Benefit Information for Prescription Drugs and Medical Devices*, June 2014, at 3,

the drug is to be dispensed) is subject to FDA's review as part of the FDA's drug approval process.⁹⁷ FDA considers promotional labeling to be any other materials that meet the definition of 'labeling' that is devised for the promotion of the product.⁹⁸ FDA interprets the category of promotional labeling to include a wide-range of written communications, including, among other things, statements made in television ads, brochures, booklets, detailing pieces, internet web sites, print ads, exhibits, and sound recordings or radio ads.⁹⁹

To satisfy FDA's mandate to promote the public health, those items that fall within the purview of the Agency's 'labeling' authority are subject to stringent safety and efficacy requirements.¹⁰⁰ As discussed in the following sections, FDA prohibits 'labeling' from discussing unapproved uses of a drug, and the Agency applies the same substantiation standard required to obtain drug approval—the 'substantial evidence' standard—when assessing labeling claims related to safety and effectiveness.

III.B The Intended Use Regulation

The 'intended uses' of a drug matter when determining whether a drug is an 'unapproved new drug' and whether a drug is labeled with 'adequate directions for use', as discussed further below. FDA's 'intended use' regulation provides the Agency with authority to reach beyond the actual FDA-approved labeling of a product to 'oral and written statements' and 'circumstances surrounding the distribution of the article'.¹⁰¹

The FDCA prohibits the introduction into interstate commerce of a new drug without FDA approval.¹⁰² If an approved drug is intended for an unapproved use, the drug is considered an unapproved new drug with respect to the unapproved use in violation of the FDCA.¹⁰³ Admittedly, the 'unapproved new drug' approach for restricting off-label promotion has limitations because the definition of 'new drug' (1) refers only to uses recommended in labeling and (2) excludes uses that are generally recognized as safe and effective.¹⁰⁴ Consequently, an 'unapproved new drug' charge likely could not be sustained for off-label promotion carried out only orally or for an off-label use that is strongly supported by the scientific literature and by established standards for clinical care.

As an additional method for restricting off-label promotion under the FDCA, a drug is 'misbranded' if its labeling fails to include 'adequate directions for use'.¹⁰⁵ FDA regulations define 'adequate directions for use' as those that allow a layperson to 'use a drug

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM401087.pdf> (accessed Apr. 10, 2015).

⁹⁷ See 21 C.F.R. § 314.50(c)(2)(i).

⁹⁸ See, e.g., FDA, *Draft Guidance for Industry: Internet/Social Media Platforms with Character Space Limitations—Presenting Risk and Benefit Information for Prescription Drugs and Medical Devices*, June 2014, at 3.

⁹⁹ See, e.g., FDA, *Draft Guidance for Industry: Presenting Risk Information in Prescription Drug and Medical Device Promotion*, May 2009, at 3 n.9, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM155480.pdf> (accessed Apr. 10, 2015).

¹⁰⁰ See, e.g., 21 C.F.R. § 201.57.

¹⁰¹ 21 C.F.R. § 201.128.

¹⁰² 21 U.S.C. § 355(a). This requirement does not apply to biological products licensed under the Public Health Service Act. See 42 U.S.C. § 262(j).

¹⁰³ See 21 C.F.R. § 310.3(h).

¹⁰⁴ 21 U.S.C. § 321(p); see Coleman, *supra* note 4, at 162.

¹⁰⁵ 21 U.S.C. § 352(f).

safely and for the purposes for which it is intended'.¹⁰⁶ Prescription drugs are technically exempt from the statutory requirement to be labeled with 'adequate directions for use' if they comply with specific regulatory requirements applicable to prescription drugs, including requirements that labeling (1) 'bears adequate information for... use' of the drug such that a licensed practitioner may 'use the drug safely and for the purposes for which it is intended, including all purposes for which it is advertised or represented';¹⁰⁷ and (2) must be the same as the FDA-approved labeling with respect to the use of the drug and must be consistent with the FDA-approved labeling with respect to any other information.¹⁰⁸ Because prescription drug labeling must match the FDA-approved labeling, a prescription drug promoted for an off-label use cannot satisfy the regulatory requirements to be exempt from the statutory requirement to be labeled with adequate directions for use. Put more simply, a prescription drug promoted for an off-label use cannot be labeled, consistent with the FDCA and FDA regulations, with adequate directions for use.¹⁰⁹

FDA implemented the intended use regulation in an effort to address the Agency's concern that manufacturers would circumvent the FDCA's labeling requirements by providing unapproved information to consumers in communications falling outside the traditional labeling definition.¹¹⁰ FDA defines 'intended uses' as referring to 'the objective intent of the persons legally responsible for the labeling of drugs'.¹¹¹ FDA explains:

The intent is determined by such persons' expressions or may be shown by the circumstances surrounding the distribution of the article. This objective intent may, for example, be shown by labeling claims, advertising matter, or oral or written statements by such persons or their representatives. It may be shown by the circumstances that the article is, with the knowledge of such persons or their representatives, offered and used for a purpose for which it is neither labeled nor advertised. The intended uses of an article may change after it has been introduced into interstate commerce by its manufacturer. If, for example, a packer, distributor, or seller intends an article for different uses than those intended by the person from whom he received the drug, such packer, distributor, or seller is required to supply adequate labeling in accordance with the new intended uses. But if a manufacturer knows, or has knowledge of facts that would give him notice, that a drug introduced into interstate commerce by him is to be used for conditions, purposes, or uses other than the ones for which he offers it, he is required to provide adequate labeling for such a drug which accords with such other uses to which the article is to be put.¹¹²

FDA often relies on the intended use regulation to argue that manufacturer communications regarding off-label uses serve as evidence of a new 'intended use' for an

¹⁰⁶ 21 C.F.R. § 201.5.

¹⁰⁷ 21 C.F.R. § 201.100(c)(1).

¹⁰⁸ *Id.* § 201.100(d)(1).

¹⁰⁹ See, e.g., Criminal Information at 4, *United States v. Par Pharm. Cos.*, No. 13-MJ-8080 (D.N.J. Mar. 5, 2013), <http://www.justice.gov/usao/nj/Press/files/pdffiles/2013/Par%20Pharmaceutical%20Information.pdf> (accessed Apr. 10, 2015) ('An FDA-approved prescription drug, bearing the FDA-approved labeling, could be exempt from the adequate-directions-for-use requirement if it was marketed for an FDA-approved use. ... A prescription drug that was marketed for non-approved, off-label uses would not qualify for this exemption and therefore would be misbranded').

¹¹⁰ See 17 Fed. Reg. 6818, 6820 (July 25, 1952).

¹¹¹ 21 C.F.R. § 201.128.

¹¹² *Id.*

approved drug. If the labeling fails to bear adequate directions for this unapproved intended use, the drug is misbranded.¹¹³ If the manufacturer includes directions for this unapproved use, then the drug is an unapproved new drug.¹¹⁴

While FDA has historically determined the intended uses of a product based on a manufacturer's representations,¹¹⁵ the intended use regulation allows FDA to consider other factors to establish intended use, including the manufacturer's knowledge that the product is being used for an unapproved purpose.¹¹⁶ In more recent years, the Agency and the Department of Justice ('DOJ') (in criminal prosecutions) have suggested that the following, among other things, may create a new intended use: (1) the known effect of a product on a user,¹¹⁷ (2) visits by sales representatives and the information conveyed during such visits,¹¹⁸ and (3) the subjective intent of the manufacturer.¹¹⁹

In sum, FDA's intended use regulation allows the Agency to proscribe virtually all speech about a drug that goes beyond the FDA-approved labeling under the theory that the drug lacks adequate directions for use, and therefore, the drug is misbranded or is an unapproved new drug. This regulatory framework effectively proscribes all off-label speech by a manufacturer.

III.C The Substantial Evidence Requirement

The 1962 amendments to the FDCA required a drug company to demonstrate the effectiveness of a new drug, rather than just safety, prior to approval.¹²⁰ Specifically, the

¹¹³ 21 U.S.C. § 352(f)(1).

¹¹⁴ 21 U.S.C. § 355(a).

¹¹⁵ See, e.g., *United States v. Hohensee*, 243 F.2d 367, 370 (3d Cir. 1957) (intended use proved by claims in graphic material as well as oral representations); *United States v. Millpax, Inc.*, 313 F.2d 152, 154 (7th Cir. 1963) (citing a 'disclaimer letter' and magazine testimonials implying that iron tonic was a cancer cure as establishing intended use); *Nature Food Centres, Inc. v. United States*, 310 F.2d 67, 69 (1st Cir. 1962) (relying on claims made in lectures and 'Class Notes on Health and Nutrition' to prove intended use); *United States v. Articles of Drug ... Foods Plus, Inc.*, 362 F.2d 923, 926 (3d Cir. 1966) (intended use established by a manufacturers' broadcast claims).

¹¹⁶ However, FDA has previously claimed that knowledge alone of an off-label use will not serve as the basis for enforcement action for the marketing of an unapproved new use of a drug. See FDA Reply Brief, *Allergan, Inc. v. United States*, Case 1:09-cv-01879-JDB (D.D.C. Mar. 29, 2010); see also Temple Dec. ¶ 9, *Allergan Inc. v. United States*, Civil Action No. 09-1879 (D.D.C. Mar. 26, 2010) (explaining that 'FDA would not ordinarily regard a manufacturer as intending an off-label use of an approved product based solely on the manufacturer's knowledge that an approved product was being used for such use, and even if the sponsor provided scientific articles about such use').

¹¹⁷ See 60 Fed. Reg. 41453, 41482 (Aug. 11, 1995) (asserting that evidence regarding nicotine's effects on smokers is evidence that it is intended for use as a drug).

¹¹⁸ See, e.g., Brief and Special Appendix for the United States, *Caronia v. United States*, 2010 WL 6351,497 (2d Cir. 2010) (describing discussions of scientific literature by sales representatives with healthcare professionals).

¹¹⁹ See Brief for the Appellants, *Washington Legal Foundation v. Henney*, 1999 WL 34834316 (D.C. Cir. 1999) (arguing that '[t]he unsolicited dissemination of such information is highly persuasive evidence that the manufacturer intends that the product be used in the unapproved manner. And if the manufacturer has not demonstrated that the intended use of the product is safe and effective, the manufacturer's continued introduction of the product into interstate commerce is unlawful as long as the manufacturer continues to intend such use'); see also Richard M. Cooper, *The WLF Case Thus Far: Not with a Bang, But a Whimper*, 55 FOOD & DRUG L.J. 477, 485 (2000) ('FDA's theory ... was that it is unlawful for a manufacturer to introduce into interstate commerce a drug that is an unapproved new drug, or that is misbranded, because the manufacturer subjectively intends the drug to be put to an off-label use.').

¹²⁰ See Pub. L. No. 87-781, 76 Stat. 780 (1962); 21 U.S.C. § 355(a), (d).

FDCA requires sponsors of new drug applications to provide ‘substantial evidence’ of a drug’s effectiveness prior to approval.¹²¹ The FDCA defines substantial evidence as:

evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof.¹²²

Relying on the plurality of terms ‘investigations, including clinical investigations’, FDA has interpreted ‘substantial evidence’ as generally¹²³ requiring ‘at least two adequate and well-controlled studies, each convincing on its own, to establish effectiveness.’¹²⁴ FDA regulations set forth detailed criteria necessary to satisfy the ‘adequate and well-controlled studies’ requirement¹²⁵ and further provide that the Agency can refuse to approve a new drug application if ‘[t]here is a lack of substantial evidence consisting of adequate and well-controlled investigations... that the drug product will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in its proposed labeling’.¹²⁶ The requirement of two adequate and well-controlled studies to establish effectiveness has come to be known as the ‘gold standard’ for FDA approval.

While the substantial evidence standard was developed in the context of drug approval, FDA regulations apply this rigorous approval standard to any claim made in a wide-range of communications made about a previously approved product, setting a high bar for manufacturers—both in time and money—to share truthful and non-misleading, up-to-date information about their products. Substantial evidence is required to support claims ‘recommended or suggested’ in drug labeling.¹²⁷ Additionally, FDA regulations indicate that an advertisement will be considered false or misleading if, for among other reasons, the advertisement represents or suggests the drug is more effective or safer than has been demonstrated by substantial evidence.¹²⁸

¹²¹ 21 U.S.C. § 355(d).

¹²² *Id.*

¹²³ FDA has the flexibility to approve a new drug application with evidence from only one clinical study along with confirmatory evidence in certain circumstances. See 21 U.S.C. § 355(d). Additionally, FDA may exercise administrative authority and approve a drug based upon preliminary evidence of effectiveness if it satisfies the ‘breakthrough therapy’ standard or qualifies for FDA’s accelerated approval review. FDA may also on a case-by-case basis approve a drug based upon one clinical trial but has generally limited such circumstances to cases involving orphan drug products or therapies to treat serious and life-threatening diseases.

¹²⁴ See FDA, *Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products*, May 1998, <http://www.fda.gov/downloads/Drugs/.../Guidances/ucm078749.pdf> (accessed Apr. 10, 2015); see also Final Decision on Benlylin, 44 Fed. Reg. 51512, 51518 (Aug. 31, 1979).

¹²⁵ 21 C.F.R. § 314.126.

¹²⁶ *Id.* § 314.125(a)(5).

¹²⁷ 21 U.S.C. § 355(d)(5); see 21 C.F.R. § 201.57(c)(2)(iii)-(v). The FDCA also considers a drug misbranded if ‘its labeling is false or misleading in any particular’. 21 U.S.C. § 352(a).

¹²⁸ 21 C.F.R. § 202.1(e)(6). Section 202.1(e)(6) technically permits such advertising claims to be supported by either substantial evidence or ‘substantial clinical experience’, which is defined as ‘experience adequately documented in medical literature or by other data ... on the basis of which it can fairly and responsibly be concluded by qualified experts that the drug is safe and effective for such uses’. 21 C.F.R. § 202.1(e)(4)(ii)(c).

As a limited exception to the generally applicable substantial evidence requirement, the FDCA authorizes manufacturers to provide to ‘a formulary committee, or other similar entity’ healthcare economic information (‘HCEI’) that ‘directly relates’ to an *approved* indication, so long as the information is based on ‘competent and reliable scientific evidence’.¹²⁹ HCEI is defined as ‘any analysis that identifies, measures, or compares the economic consequences, including the costs of the represented health outcomes, of the use of a drug to the use of another drug, to another healthcare intervention, or to no intervention’.¹³⁰ Nonetheless, despite the existence of this statutory HCEI exception, at least one senior FDA official in the Center for Drug Evaluation and Research takes the position that ‘clinical outcomes assumptions’ used as the basis for HCEI claims must still be based on substantial evidence.¹³¹ This interpretation greatly limits the ability of drug manufacturers to make HCEI claims without substantial evidence to support them because drug manufacturers frequently do not have clinical outcomes data from head-to-head, adequate, well-controlled trials comparing the treatments that form the basis for the HCEI claim.

Generally, FDA only directly applies the substantial evidence standard to ‘on-label statements’, choosing instead to regulate off-label claims by the ‘intended use’ analysis discussed in part III.B, *supra*. However, under the Agency’s asserted broad authority over promotional labeling—which includes nearly all materials that mention a product’s name—FDA has effectively created a regulatory structure in which any written statements related to efficacy that a manufacturer creates about a particular product fall within FDA’s regulatory authority and therefore need to be substantiated by two adequate and well-controlled clinical trials. As further discussed in part IV, *infra*, this strict substantiation requirement restricts manufacturers from disseminating a significant amount of truthful and non-misleading information.

III.D The Lack of Regulatory Clarity

Despite the statutory and regulatory framework described above that could be interpreted as categorically prohibiting off-label promotion, FDA has acknowledged in one regulation that certain types of manufacturer communications fall outside the Agency’s reach and are not prohibited. In a regulation addressing the promotion of investigational new drugs, FDA states:

A sponsor or investigator, or any person acting on behalf of a sponsor or investigator, shall not represent in a promotional context that an investigational new drug is safe or effective for the purposes for which it is under investigation or otherwise promote the drug. This

Despite the apparent flexibility that the substantial clinical experience standard should provide, the regulation seemingly limits the application of the standard only to drugs that have not been approved by FDA but that are not considered ‘new drugs’. See §§ 202.1(e)(4)(ii) (excluding ‘drugs covered by paragraph (e)(4)(i)’ from its scope), 202.1(e)(4)(i) (applying paragraph to drugs approved by FDA after and before 1962).

¹²⁹ *Id.*

¹³⁰ 21 U.S.C. § 352(a).

¹³¹ See Robert Temple, *Communication of CER Findings*, Feb. 9, 2012, at 14 (presentation at ‘Asymmetry in the Ability to Communicate CER Findings: Ethics and Issues for Informed Decision Making’ conference hosted by the National Pharmaceutical Council), http://www.npcnow.org/system/files/conferences/download/rtemple_asym12.pdf (accessed Apr. 10, 2015).

provision is not intended to restrict *the full exchange of scientific information* concerning the [investigational] drug, including dissemination of scientific findings in scientific or lay media.¹³²

The regulation does not elaborate upon the scope or definition of scientific exchange, and the Agency has never clearly defined the scope of materials or manufacturer communications that fall under the umbrella of scientific exchange.¹³³ Furthermore, the regulation is difficult to interpret because of its use of the term ‘promotional’, which FDA has never defined. FDA has also never specified whether the regulation applies to drugs that are not subject to an investigational new drug application.

FDA’s lack of specificity to date regarding the scope of permissible scientific exchange and numerous other aspects of its regulatory framework (e.g., the evidence needed to support an HCEI claim) leaves manufacturers with little guidance regarding their ability to communicate truthful and non-misleading scientific information to healthcare professionals, payors, and other key stakeholders. Although the regulatory schemes of many administrative agencies include vague or undefined terms, the FDA’s regulatory framework is especially difficult to interpret and apply because of how inter-related the various unclear terms and provisions are to one another. In our experience as practitioners, this lack of regulatory clarity has forced manufacturers to develop their promotional compliance policies and processes by attempting to ‘read the tea leaves’ through FDA enforcement letters and non-binding statements from the Agency and other government officials as well as publicly available documents from government settlements with drug manufacturers.¹³⁴ For example, a government prosecutor stated at a public conference that relevant factors in determining whether to prosecute a manufacturer for off-label promotion include: (1) the size of the total market for the approved uses of the drug and (2) whether the manufacturer promotes the drug to doctors who do not treat patients suffering from the diseases or conditions covered by the approved uses of the drug.¹³⁵ FDA has never spoken formally on either of these issues. The consequence of the ‘read the tea leaves’ approach is that the tea leaves may be read incorrectly, which can result in either unintended adverse judgments and penalties or unnecessary inaction.

III.E Recent Regulatory and Policy Developments

FDA has recently begun to recognize to some degree the lack of clarity and flexibility in its promotional policies and has taken strides in recent years to rectify some of these concerns via one-off guidance documents addressing certain safe harbors that, although FDA had acknowledged their existence for some time, had not previously been well-defined. These guidance documents include:

¹³² 21 C.F.R. § 312.7(a) (emphasis added).

¹³³ *Id.*

¹³⁴ See *Citizen Petition from MIWG*, Docket No. FDA-2011-P-0512, July 5, 2011, at 9, <http://www.regulations.gov/#1documentDetail;D=FDA-2011-P-0512-0001> (accessed Apr. 10, 2015).

¹³⁵ See Michael Loucks, *Trends in Prosecutions and So-Called Off-Label Promotion Issues*, Nov. 26, 2007, <http://www.ehcca.com/presentations/pharmaaudio20071126/loucks.pdf> (accessed Apr. 10, 2015).

- A final guidance in 2009¹³⁶ and a revised draft guidance in 2014¹³⁷ addressing manufacturer dissemination of scientific publications, including medical journal articles, reference texts, and clinical practice guidelines, addressing off-label uses. Under the Revised Draft Reprints Guidance, drug manufacturers are limited to providing articles based on adequate and well-controlled studies, even though device manufacturers—but not drug manufacturers—are permitted to distribute articles based on other scientific evidence, such as meta-analyses, pharmacokinetic and pharmacodynamics studies, or significant non-clinical research.¹³⁸ FDA offers no rationale for this distinction. Additionally, the Revised Draft Reprints Guidance permits the dissemination of clinical practice guidelines ('CPGs') but only if they meet certain rigorous criteria, including that the CPG 'be based on a systematic review of the evidence' (which FDA does not define) and that the CPG must satisfy standards for 'trustworthiness' established by the Institute of Medicine (even though one recent review of 169 oncology-related CPGs found that none of the CPGs satisfied the IOM standards).¹³⁹
- A draft guidance in 2011 addressing how manufacturers may respond to unsolicited requests for off-label information.¹⁴⁰ Under this Unsolicited Requests Draft Guidance, a request is considered 'unsolicited' only if initiated by persons or entities 'completely independent' of the drug manufacturer and not 'prompted in any way by a manufacturer or its representatives'.¹⁴¹ The document also distinguishes between 'public' and 'non-public' (i.e., one-on-one) unsolicited requests. FDA asserts that a manufacturer is not permitted to provide any substantive off-label information in response to a public request; instead, the manufacturer is only permitted to invite the requestor to follow up with the manufacturer's medical or scientific affairs department to make a 'non-public' request.¹⁴² This limitation on a manufacturer's ability to communicate truthful and non-misleading information simply because the communication occurs in a public forum raises both constitutional and policy concerns.¹⁴³

¹³⁶ 2009 Reprints Guidance, *supra* note 8.

¹³⁷ FDA, *Revised Draft Guidance for Industry: Distributing Scientific and Medical Publications on Unapproved New Uses—Recommended Practice*, Feb. 2014, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM387652.pdf> (accessed Apr. 10, 2015) (hereinafter 'Revised Draft Reprints Guidance'). Unlike the 2009 Reprints Guidance, the Revised Draft Reprints Guidance permits the dissemination of CPGs meeting certain rigorous criteria. *Id.* at 14, 17.

¹³⁸ *Id.* at 7, 8.

¹³⁹ *Id.* at 11, 14. See Bradley N. Reames et al., *Clinical Evaluation of Oncology Clinical Practice Guidelines*, 31 J. CLIN. ONCOLOGY 2563, 2563–65 (2013).

¹⁴⁰ FDA, *Draft Guidance for Industry: Responding to Unsolicited Requests for Off-Label Information About Prescription Drugs and Medical Devices*, Dec. 2011, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM285145.pdf> (accessed Apr. 10, 2015) (hereinafter 'Unsolicited Requests Draft Guidance').

¹⁴¹ *Id.* at 4.

¹⁴² *Id.* at 11.

¹⁴³ See, e.g., Bagley et al., *supra* note 67, at 384 ('[T]he rationale behind the public/nonpublic dichotomy seems questionable. ... [T]he costs and benefits of off-label information dissemination seem to have less connection to the public nature of the request as to the truth versus falsehood of the information.').

- A draft guidance in 2014 addressing the circumstances when a manufacturer may disseminate scientific publications discussing risk information that is inconsistent with the FDA-approved labeling for the drug.¹⁴⁴ Under this Risk Information Draft Guidance, drug manufacturers are permitted to communicate new risk information about a drug based on, among other things, a pharmacoepidemiologic study or a rigorous meta-analysis, that may rebut or mitigate risk information in the approved labeling.¹⁴⁵ This guidance appears to establish an exception to the Agency's substantial evidence rule,¹⁴⁶ but FDA does not explicitly acknowledge that its non-binding guidance is somehow intended to overrule a binding regulation.¹⁴⁷

Importantly, none of the guidance documents provide any discussion of how FDA's regulatory framework and policies comport with the First Amendment. They also do not address a number of other significant areas of ambiguity, such as communications with payors and formulary committees or the scope of permissible scientific exchange more broadly. The recent guidances also do not alter existing statutory and regulatory requirements and, at least according to their express terms, do not 'bind FDA or the public'.¹⁴⁸ Rather, if a manufacturer follows the recommendations provided by these guidance documents, 'FDA does not intend to object' to the manufacturer's actions and 'does not intend' to use the manufacturer's actions as evidence of a new, unapproved intended use for a product.¹⁴⁹ Such language indicates that FDA believes these practices do not technically comply with the FDCA and FDA regulations but may be permissible

¹⁴⁴ FDA, *Draft Guidance for Industry: Distributing Scientific and Medical Publications on Risk Information for Approved Prescription Drugs and Biological Products—Recommended Practices*, June 2014, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM400104.pdf> (accessed Apr. 10, 2015) (hereinafter 'Risk Information Draft Guidance').

¹⁴⁵ *Id.* at 6, 7.

¹⁴⁶ See 21 C.F.R. § 202.1(e)(6).

¹⁴⁷ FDA's recent issuance of a revised draft guidance on the communication of risk information in consumer-directed advertisements provides a similar example of FDA apparently attempting to overrule a regulation via a non-binding guidance. See FDA, *Revised Draft Guidance for Industry: Brief Summary and Adequate Directions for Use: Disclosing Risk Information in Consumer-Directed Print Advertisements and Promotional Labeling for Human Prescription Drugs*, Feb. 2015, <http://www.fda.gov/downloads/drugs/guidancecompliance/regulatoryinformation/guidances/ucm069984.pdf> (accessed Apr. 10, 2015) (hereinafter 'Revised Draft Brief Summary Guidance'). Under FDA's advertising regulations, all prescription drug advertisements must contain a 'brief summary relating to ... side effects, warnings, precautions, and contraindications ... and effectiveness'. 21 C.F.R. § 202.1(e)(1). The Revised Draft Brief Summary Guidance expressly recommends against this 'traditional approach' spelled out in the regulations and instead proposes that consumer-directed advertisements 'should focus on the most important risk information rather than an exhaustive list of risks'. Revised Draft Brief Summary Guidance, at 4.

¹⁴⁸ E.g., *id.* at 1; see 21 C.F.R. § 10.115(d)(1) ('Guidance documents do not establish legally enforceable rights or responsibilities. They do not legally bind the public or FDA').

¹⁴⁹ See *id.* at 6 ('FDA does not intend to object to the distribution of new risk information that rebuts, mitigates, or refines risk information in the approved labeling, and is distributed by a firm in the form of a reprint or digital copy of a published study, if the study or analysis and the manner of distribution meet the principles set out below. '); Revised Draft Reprints Guidance, *supra* note 137, at 6 ('[I]f manufacturers distribute scientific or medical publications as recommended in this guidance, FDA does not intend to use such distribution as evidence of the manufacturer's intent that the product be used for an unapproved new use. '); Unsolicited Requests Draft Guidance, *supra* note 140, at 3 ('If a firm responds to unsolicited requests for off-label information in the manner described in this draft guidance, FDA does not intend to use such responses as evidence of the firm's intent that the product be used for an unapproved ... use.').

under the Agency's exercise of enforcement discretion.¹⁵⁰ Nonetheless, FDA's apparent 'narrow carve-outs' from otherwise applicable promotional restrictions are unlikely to save FDA's current regulatory framework from a First Amendment challenge.¹⁵¹ Additionally, because the guidance documents claim to not even be binding on FDA, they are also non-binding on the DOJ—the entity responsible for actually prosecuting violations of the FDCA.¹⁵²

FDA has released the recent guidance documents at least partially in response to recent citizen petitions. In July 2011, seven members of the Medical Information Working Group ('MIWG'), a consortium of certain pharmaceutical and medical device manufacturers, filed a citizen petition requesting an explanation of the contours of certain promotional safe harbors.¹⁵³ In March 2012, in response to questions posed by FDA on the meaning of scientific exchange,¹⁵⁴ the MIWG commented that FDA had no authority to regulate scientific exchange, and that FDA should more carefully define labeling and advertising to be mindful of statutory and constitutional limitations.¹⁵⁵ Then, in September 2013, the MIWG filed another citizen petition reiterating the manufacturers' request that the Agency provide clarity with respect to the promotional safe harbors, and also asked the Agency to reconsider its regulatory regime in light of new First Amendment case law,¹⁵⁶ particularly with respect to the definitions of 'labeling', 'advertising', and 'intended use'.¹⁵⁷ In June 2014, the Agency granted the MIWG's citizen petition and committed to a 'comprehensive review of its regulations and guidance documents in an effort to harmonize the goal of protecting the public health with First Amendment interests'.¹⁵⁸

IV. THE NEED FOR A NEW REGULATORY MODEL AND ITS OBJECTIVES

Today, drug manufacturers communicate with healthcare professionals by many avenues: traditional office-based and hospital-based detailing, journal advertising, Internet promotion, and medical conferences and meetings, among others.¹⁵⁹

¹⁵⁰ See generally Lars Noah, *Governance by the Backdoor: Administrative Law (lessness?) at the FDA*, 93 NEB. L. REV. 89 (2014) (describing FDA's increasing practice of issuing technically non-binding guidance documents as procedural short cuts to notice-and-comment rulemaking, as well as the coercive effect these guidance documents have on regulated industry).

¹⁵¹ Cf. Noah, *supra* note 47, at 75 ('It seems doubtful, however, that these narrow carve-outs would save an otherwise problematic ban on advertising to physicians.').

¹⁵² See 21 U.S.C. § 337(a) ('[A]ll such proceedings for the enforcement, or to restrain violations, of [the FDCA] shall be by and in the name of the United States.').

¹⁵³ *Citizen Petition from MIWG*, Docket No. FDA-2011-P-0512 July 5, 2011, <http://www.regulations.gov/#!documentDetail;D=FDA-2011-P-0512-0001> (accessed Apr. 10, 2015).

¹⁵⁴ 76 Fed. Reg. 81,508, 81,509 (Dec. 28, 2011).

¹⁵⁵ See *Comments of the Medical Information Working Group on Scientific Exchange and Responses to FDA Unsolicited Requests*, Docket Nos. FDA-2011-N-0912 and -2011-D-0868, Mar. 27, 2012, at 2, <http://www.regulations.gov/#!documentDetail;D=FDA-2011-N-0912-0015> (accessed Apr. 10, 2015).

¹⁵⁶ See *supra* part II.C.

¹⁵⁷ *Citizen Petition from MIWG*, Docket No. FDA-2013-P-1079, Sept. 3, 2013, <http://www.regulations.gov/#!documentDetail;D=FDA-2013-P-1079-0001> (accessed Apr. 10, 2015).

¹⁵⁸ *Citizen Petition Response to MIWG*, Docket Nos. FDA-2013-P-1079 and FDA-2011-P-0512, June 6, 2014, at 8, <http://www.regulations.gov/#!documentDetail;D=FDA-2013-P-1079-0004> (accessed Apr. 10, 2015).

¹⁵⁹ Rachel Kornfield et al., *Promotion of Prescription Drugs to Consumers and Providers, 2001–2010*, PLOS ONE, Mar. 2013, at 2, <http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0055504#pone-0055504-t005> (accessed Apr. 10, 2015). In addition, manufacturers also engage in direct-to-consumer advertising in television, print, Internet, and other media. *Id.*

Manufacturers also increasingly rely on medical science liaisons (‘MSLs’), specialized employees with advanced degrees and scientific training, to disseminate medical information to healthcare professionals, payors, and formulary committees (to the extent permitted by FDA) and to engage healthcare professionals regarding mutual clinical interests and the dynamics and unmet needs in the medical community.¹⁶⁰ Many of these communication methods were not contemplated when the FDCA was enacted and when the FDA’s restrictive regulatory framework was originally established. FDA’s restrictions on even truthful and non-misleading manufacturer speech fail to recognize the full potential of these modern communication methods to meet the urgent need in the medical community for accurate, up-to-date information about drugs to guide patient care.

In the area of scientific exchange and the communication of off-label information by manufacturers, FDA’s constrained rules do not always serve the public health. The FDA’s effort to constrain the communication of off-label information runs counter to the clinician’s need for access to the latest clinical research and insights. FDA’s current regulatory framework also conflicts with the First Amendment by imposing significant speaker-based and content-based limitations on manufacturers’ ability to communicate important medical information.

We believe a new regulatory framework—a New Model—is necessary to address the limitations of the current framework and to permit more truthful and non-misleading communications by manufacturers. The New Model seeks to achieve the following five objectives:

1. Protect the public health, consistent with FDA’s mission, by ensuring healthcare professionals, payors, and other healthcare decision-makers have access to accurate, up-to-date information about drugs while at the same time ensuring that promotional communications accurately describe information submitted to FDA as the basis for approval;
2. Comport with the First Amendment protections afforded to drug manufacturers as emphasized by *Sorrell*, *Caronia*, and related cases;
3. Establish understandable and translatable rules so that manufacturers are on fair notice of what is required of them and healthcare professionals, payors, and other recipients of such information understand the context of what is being communicated;
4. Maintain the FDA approval process as the ‘gold standard’ around the world while permitting truthful and non-misleading statements that may not meet the rigorous FDA approval standard; and
5. Promote the development of new uses and maintain appropriate incentives to entry.

IV.A Protect the Public Health

By significantly limiting the dissemination of useful knowledge by manufacturers about their drugs, FDA’s restrictions on truthful and non-misleading speech actually conflict with FDA’s public health mission. FDA itself openly recognizes the ‘the important

¹⁶⁰ Jennifer L. Bass et al., *Survey Medical Liaison Practices 3: Assessing Practice Trends Across the Pharmaceutical Industry*, 44 DRUG INFO. J. 535, 535 (2010).

public health and policy justification supporting dissemination of truthful and non-misleading' scientific literature addressing off-label uses and even acknowledges that off-label uses 'may be important and may even constitute a medically recognized standard of care'.¹⁶¹ Off-label use is not only highly prevalent but often critical for patient care. 50–75 per cent of all oncology drug use is estimated to be off-label,¹⁶² and off-label use is also highly prevalent for the treatment of heart disease, AIDS, kidney disease, osteoporosis, and psychiatric illnesses.¹⁶³ One study published in 2006 estimated 21 per cent of all drug use is off-label.¹⁶⁴ Additionally, 'medically accepted' off-label uses are reimbursed by federal healthcare programs.¹⁶⁵ Off-label treatment is often the only option for pediatric patients or patients with orphan diseases where no FDA-approved drug is available.¹⁶⁶ Off-label treatment also plays a key role in clinical innovation, given the time, delay, and expense in seeking FDA approval for a new indication or change in the label, and such innovative flexibility is especially important when no approved treatment regimen is available to or effective for a patient.¹⁶⁷ Therefore, 'open dissemination of scientific and medical information' on off-label use is critical to furthering the public health.¹⁶⁸

Further examples of the beneficial impact of off-label information include the clinical management of patients suffering from infection with HIV, hepatitis B virus, or hepatitis C virus.¹⁶⁹ Very soon after single drugs were approved by the FDA to treat patients with HIV infection, investigators, clinicians, patient advocates, and others quickly collaborated to identify and use more effective off-label, multidrug combinations. Reports of rapidly advancing clinical research demonstrated that three-agent

¹⁶¹ 2009 Reprints Guidance, *supra* note 8; see Unsolicited Requests Draft Guidance, *supra* note 140, at 2.

¹⁶² See Soares, *supra* note 9, at 104 (2005) (stating that '50% to 75% of all uses of drugs and biologics in cancer care in the United States are off-label'); Beck & Azari, *supra* note 9, at 80 n.76, 85 (noting that '[m]ore than 80% of AIDS patients are treated with at least one drug being prescribed off-label, and more than 40% of all drugs prescribed for AIDS treatment are prescribed off-label'); Barron, *supra* note 9, at 988, 989 (2011) ('[M]ore than half of all cancer patients receive off-label treatments not only because cancer treatment is constantly evolving, but also because patients who are running out of options push for experimental treatments.') (internal citations omitted).

¹⁶³ Stafford, *supra* note 9, at 1427; Beck & Azari, *supra* note 9, at 80.

¹⁶⁴ See David C. Radley et al. *Off-label Prescribing Among Office-Based Physicians*. 166 ARCH INTERN MED. 1021, 1021 (2006) (reporting estimates of off-label used based on data from the 2001 IMS Health National Disease and Therapeutic Index).

¹⁶⁵ See 42 U.S.C. §§ 1396r-8(d)(1)(8)(i), (k)(6), (g)(1)(8)(i).

¹⁶⁶ Stafford, *supra* note 9, at 1427 (noting that off-label drugs 'can provide the only available treatments for "orphan" conditions'); Beck & Azari, *supra* note 9, at 80 ('Off-label use is extensively used in cases of rare diseases.').

¹⁶⁷ See Stafford, *supra* note 9, at 1427 (noting that off-label use "permits innovation in clinical practice, particularly when approved treatments have failed"); *Promotion of Drugs and Medical Devices for Unapproved Uses: Hearing Before the Human Resources and Intergovernmental Relations Subcomm. of the House Comm. on Gov't Operations*, 102d Cong., 1st Sess. 103 (1991) (statement of George Lundberg, M.D.) ("There are too many variations in clinical circumstances and too much time delay in regulations to allow the government to impede the physician's ability to practice in these regards when it is medically appropriate.").

¹⁶⁸ Kristie LaSalle, *A Prescription for Change: Citizens United's Implications for Regulation of Off-Label Promotion of Prescription Pharmaceuticals*, 19 J.L. & POL'Y 867, 902–03, 906–07 (2011) (claiming that '[p]hysicians' prescribing decisions, and therefore the public health, will be improved if physicians are well-informed about potential off-label uses' and that '[t]he FDA's policy of absolute suppression of manufacturer dissemination of this information frustrates, rather than serves, the interest of enhancing and protecting public health').

¹⁶⁹ See Andrew Aronsohn et al., *Preparing for the Uncertain yet Inevitable: Off-Label Combinations of Antiviral Agents in Hepatitis C Virus*, 59 HEPATOLOGY 1688 (2014).

combinations were highly effective regimens and, thus, they were quickly adopted into clinical practice and became the standard of care prior to FDA approval of the combination uses. The HIV/AIDS experience, underscores the importance of information exchange in accelerating the sharing of clinical insights and enhancing quality of care and related outcomes. Additionally, the fact that off-label drug use can be efficiently detected using automated information technology systems means that potentially beneficial off-label uses gleaned from prescribing data can be effectively prioritized for more in-depth, scientifically rigorous clinical research.¹⁷⁰

Certainly, not all off-label uses of approved drugs ultimately prove beneficial for patients and the public health, so special care must be taken to ensure that communications regarding off-label uses are based on the most current, accurate, and complete scientific information and clinical experience available and accurately disclose the limitations of existing data. In discussing risks associated with off-label uses, FDA officials routinely cite several examples of drugs that were widely used off-label but later found to be unsafe or ineffective.¹⁷¹ Yet, these examples do not counsel in favor of an outright ban on off-label prescribing, or even an outright ban on manufacturer communications regarding off-label uses. As other statements by FDA on the value of off-label uses¹⁷² and the HIV/AIDS example discussed above demonstrate, the benefits of off-label uses frequently outweigh the risks, and off-label uses can further the public health. Although the best evidence for drug efficacy and safety is typically one or more adequate, well-controlled studies, such evidence may not be practical to obtain in many cases. Moreover, other types of evidence, such as meta-analyses, observational studies, and real-world evidence, are valuable to healthcare professionals, payors, and other stakeholders not only for assessing effectiveness but also for assessing cost and utilization of drugs.

To limit the likelihood that off-label uses are adopted by the medical community that ultimately are found to be unsafe or ineffective, healthcare professionals should be informed of the most accurate, up-to-date data regarding off-label uses and made aware of the relevant limitations of the data (e.g., is the off-label use supported by a rigorous meta-analysis of adequate, well-controlled studies, or is the off-label use supported only by anecdotal evidence consisting of a few case reports?). Access to *more* information regarding off-label uses—provided that such information is truthful and non-misleading, and reflects the current state of the science—actually furthers the public health by ensuring that healthcare professionals determine whether to prescribe a drug off-label based on the best evidence currently available.¹⁷³

¹⁷⁰ See Kenneth Jung et al., *Automated Detection of Off-Label Drug Use*, PLOS ONE, Feb. 2014, <http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0089324> (accessed Apr. 10, 2015).

¹⁷¹ See, e.g., 59 Fed. Reg. 59,820, 59,824 (Nov. 18, 1994) (discussing the prescribing of anti-arrhythmic agents for improved survival post-infarction, the prescribing of calcium-channel blockers for post-infarction use, and the prescribing of BOTOX for cosmetic purposes); Decl. of Dr. Rachel E. Sherman at 9–11, *Par Pharm. Inc. v. United States*, No. 1:11-cv-1820 (D.D.C. June 28, 2012) (discussing, among other examples, the prescribing of Premarin and Prempro for prevention of coronary artery disease post-menopause, the prescribing of the anti-arrhythmic agents encainide and flecainide for improved survival post-infarction, and the prescribing of erythropoiesis stimulating agents to increase hemoglobin levels beyond normal levels).

¹⁷² See 2009 Reprints Guidance, *supra* note 8; Unsolicited Requests Draft Guidance, *supra* note 140, at 2.

¹⁷³ See Lasalle, *supra* note 168, at 907.

In general, manufacturers are in the best position to disseminate information about their own products.¹⁷⁴ They are the ‘most efficient aggregators of information about their products’¹⁷⁵ and may be able to provide the timeliest data.¹⁷⁶ Critics of off-label communications by manufacturers have argued that even though manufacturers maintain that off-label communications are ‘truthful’, these communications may not ‘provide the *whole truth*’ and may present information ‘in a manner that is inherently fraudulent or misleading’.¹⁷⁷ But even assuming that information dissemination by firms is driven by profit considerations, as critics have argued,¹⁷⁸ a manufacturer’s economic interest does not counsel in favor of absolute suppression of the manufacturer’s speech. Rather, it just means that policies should ensure the accuracy of the information communicated. Accordingly, in implementing our proposed New Model, FDA should ensure that information is communicated by manufacturers along with all relevant assumptions and limitations to promote an understanding of the objectivity of the information.¹⁷⁹

FDA’s framework essentially limits manufacturers to communicating only information that is contained in the FDA-approved labeling. This FDA-approved labeling represents a frozen ‘snapshot in time’ that reflects the state of information at the time of approval, but it may not be updated to reflect new clinical studies and new findings in peer-reviewed publications about the drug. Because healthcare professionals lack the benefit of the learning about an off-label use from the label,¹⁸⁰ they have to look elsewhere for accurate, up-to-date information about the safe and appropriate use of a drug.¹⁸¹

These other sources of information may include ‘academic detailers’ (also known as ‘counter detailers’), pharmacy benefits managers, and payors whose primary focus

¹⁷⁴ Barron, *supra* note 9, at 1010 (‘Restrictions on manufacturer speech are particularly harmful because manufacturers are often the most knowledgeable about their products.’).

¹⁷⁵ LaSalle, *supra* note 168, at 906.

¹⁷⁶ Glenn C. Smith, *Avoiding Awkward Alchemy – In the Off-Label Drug Context and Beyond: Fully-Protected Independent Research Should Not Transmogrify Into Mere Commercial Speech Just Because Product Manufacturers Distribute It*, 34 WAKE FOREST L. REV. 963, 971 (1999) (‘Manufacturer circulation of off-label research could result in such information coming into physician hands in a more timely and accessible way.’); *Citizen Petition from MIWG, Docket No. FDA-2011-P-0512*, July 5, 2011, at 5 and 6 (quoting More Information for Better Patient Care: Hearing of the Senate Comm. on Labor and Human Resources, 104th Cong. 81 (1996) (statement of Dr Gregory H. Reaman, Director, Medical Specialty Services, Children’s National Medical Center) (‘Pharmaceutical and biotechnology companies ... happen to be in the best position to share information with the physician community at the earliest possible time, when it may really make a difference in treatment options.’)), <http://www.regulations.gov/#!documentDetail;D=FDA-2011-P-0512-0001> (accessed Apr. 10, 2015).

¹⁷⁷ Stephanie M. Greene, *After Caronia: First Amendment Concerns in Off-Label Promotion*, 51 SAN DIEGO L. REV. 645, 647–48 (2014) (emphasis in original).

¹⁷⁸ Rebecca S. Eisenberg, *The Role of the FDA in Innovation Policy*, 13 MICH. TELECOMM & TECH. L. REV. 345, 374 (2007).

¹⁷⁹ See, e.g., Louis P. Garrison et al., *Using Real-World Data for Coverage and Payment Decisions: The ISPOR Real-World Data Task Force Report*, 10 VALUE HEALTH 326 (2007) (calling for good research practices for collecting and reporting real world data as an example of principles that could be incorporated in the regulatory process as a basis for information dissemination).

¹⁸⁰ LaSalle, *supra* note 168, at 906.

¹⁸¹ Beck and Azari, *supra* note 9, at 103 (noting that ‘[m]edical and other groups have complained that physicians cannot get the information they need because of FDA’s overly restrictive rules’).

is reducing healthcare costs.¹⁸² Academic detailers may communicate with healthcare professionals, formulary committees, and payors regarding comparative effectiveness research ('CER') for a drug, which may be based on meta-analyses, observational studies, clinical trial registries, and other real-world evidence¹⁸³ that do not, standing alone, satisfy FDA's 'substantial evidence' standard.¹⁸⁴ The practice of academic detailing is not subject to FDA regulations and is otherwise generally unregulated,¹⁸⁵ even though in many cases it is funded by government entities.¹⁸⁶ The asymmetry in the communication of information by academic detailers versus manufacturers does not serve the public health because it may result in healthcare professionals and patients receiving incomplete or inaccurate information about a drug—potentially jeopardizing the safe and accurate use of the product. While academic detailers and other entities may freely disseminate CER findings regarding a drug, and may be financially motivated to do so, manufacturers may be unable to respond to such findings out of fear of incurring a misbranding or off-label promotion charge.¹⁸⁷

The New Model attempts to address these concerns by enabling manufacturers to communicate critical medical information relating to the safety and effectiveness of off-label uses with healthcare professionals. Enhanced communications will promote the public health by ensuring medical decision-making is based on the most current and accurate information available. At the same time, the New Model would preserve FDA's exacting communication standards in traditional promotional contexts, such as a detailing visit by a sales representative to a healthcare professional's office.

IV.B Comport with the First Amendment

FDA's current regulatory framework raises significant First Amendment concerns and does not comport with current Supreme Court precedent. As discussed in part II, drug manufacturer speech is generally considered commercial speech for purposes of First Amendment analysis. Commercial speech in its truest, simplest form 'does no more than propose a commercial transaction'¹⁸⁸ and relates 'solely to the economic interests

¹⁸² See Joshua D. Lenchus, *A Federal Unsales Force?: 'Academic Detailing' on Medical Treatments and the Oversight Imperative*, The Washington Legal Foundation Backgrounder, Apr. 22, 2011, <http://www.cohealth.com.org/wp-content/uploads/2011/07/click-here.pdf> (accessed Apr. 10, 2015).

¹⁸³ See *id.* (noting that the several organizations receive millions of dollars from the Agency for Healthcare Research and Quality ('AHRQ') to conduct academic detailing, with little oversight over such activities); National Research Center for Academic Detailing, *About Academic Detailing*, <http://www.narcad.org/about/aboutad/> (accessed Apr. 10, 2015) (defining 'academic detailing' as 'a method of outreach education that combines the interactive, one-on-one communication approach of industry detailers with the evidence-based, noncommercial information of academia').

¹⁸⁴ See *supra* part III.C.

¹⁸⁵ See Lenchus, *supra* note 182, at 3.

¹⁸⁶ See *id.* at 2 (describing federal funding of CER and other academic detailing initiatives through AHRQ, as well as the Patient-Centered Outcomes and Research Institute established under the Patient Protection and Affordable Care Act); Cory L. Andrews, *The Rise of the Pharmaceutical Un-Sales Force*, FORBES Apr. 25, 2011, <http://www.forbes.com/sites/docket/2011/04/25/the-rise-of-the-pharmaceutical-un-sales-force/> (accessed Apr. 10, 2015) (noting funding of academic detailing by Pennsylvania and South Carolina).

¹⁸⁷ See *Comments of the MIWG on Scientific Exchange and Responses to Unsolicited Requests*, Docket Nos. FDA-2011-N-0912 and FDA-2011-D-0868, Mar. 27, 2012 (describing this as an 'asymmetrical scheme' and noting that the 'uncertainty in the regulatory scheme prevents [manufacturers]' from rebutting CER), <http://www.regulations.gov/#!documentDetail;D=FDA-2011-N-0912-0015> (accessed Apr. 10, 2015).

¹⁸⁸ *Bolger v. Youngs Drug Prods. Corp.*, 463 U.S. 60, 66 (1983) (internal quotations omitted).

of the speaker and its audience'.¹⁸⁹ Many materials that constitute 'labeling' under the FDCA,¹⁹⁰ such as package inserts, product brochures, and detailing pieces, clearly fall within this commercial speech framework because they are provided to a healthcare professional to propose a commercial transaction or provided with the drug itself as part of an immediate commercial transaction. The government's interest in restricting drug manufacturer speech is strongest for these types of 'labeling' materials.

However, not all manufacturer communications and not all materials that might qualify as 'labeling' under the FDA's expansive interpretation directly propose an immediate commercial transaction. Although all manufacturer communications may be at least in some part commercially-motivated, some communications do far more than propose a commercial transaction. For example, the distribution of a medical reprint about a drug by a manufacturer to a healthcare professional is intended primarily to educate, rather than propose an immediate sale of the drug. In the Revised Draft Reprints Guidance, FDA recognizes the value of 'truthful and non-misleading scientific or medical publications on unapproved new uses' and implicitly acknowledges the educational, rather than promotional, nature of this activity by recommending that a reprint be distributed separately from information that is 'promotional in nature'.¹⁹¹ Accordingly, the distribution of the medical reprint by the manufacturer should be considered a mix of both commercial and 'non-commercial' speech. The government's interest in regulating the non-commercial aspects of drug manufacturer speech (i.e., dissemination of truthful and non-misleading medical information) is certainly weaker than the government's interest in regulating purely commercial speech.

FDA's current regulatory framework conflicts with the First Amendment under the rationale of *Sorrell* and *Caronia* by imposing significant speaker-based and content-based restrictions on manufacturers' ability to communicate important medical information.¹⁹² The Supreme Court in *Sorrell* emphasized that government regulations disfavoring a specific type of speech (i.e., marketing) as expressed by specific parties (i.e., pharmaceutical manufacturers) are subject to heightened scrutiny and presumptively unconstitutional.¹⁹³ The FDA's restrictions are speaker-based because they only apply to the manufacturer of the drug; healthcare professionals, academics, and other speakers are free to discuss off-label uses of a drug.¹⁹⁴ Indeed, the volume of information about drugs disseminated on the Internet and via social media for healthcare professionals and consumer audiences is staggering, yet the FDA restricts the ability of drug manufacturers to partake in these valuable discussions. The FDA's restrictions are also

¹⁸⁹ *Central Hudson Gas & Elec. Corp. v. Public Serv. Comm'n*, 447 U.S. 557, 561 (1980).

¹⁹⁰ 21 U.S.C. § 321(m); see *supra* part III.A. As the Supreme Court in *Kordel* held, materials that serve as an 'essential supplement' to the package label (e.g., by explaining the uses of the drug) qualify as 'labeling'. *Kordel v. United States*, 335 U.S. 345, 348–350 (1948).

¹⁹¹ Revised Draft Reprints Guidance, *supra* note 137, at 6, 8.

¹⁹² See *Sorrell v. IMS Health Inc.*, 131 S. Ct. 2653, 2666–70 (2011); *United States v. Caronia*, 703 F.3d 149, 164–69 (2d Cir 2012).

¹⁹³ See *Sorrell*, 131 S. Ct. at 2666, 2670.

¹⁹⁴ *Caronia*, 703 F.3d at 165. But see Bagley et al. *supra* note 67, at 355, 358 (arguing that there is a distinction between a law that discriminates between industry participants 'in an arbitrary and unfair manner', like the state law at issue in *Sorrell* that discriminated between brand name and generic drug manufacturers, and a law that regulates 'its functionally justified target', such as the FDA's promotional framework, which applies to all drug manufacturers).

content-based because they prohibit off-label speech, and other speech with respect to drugs and biologics that is not supported by substantial evidence.¹⁹⁵

Relying on *Sorrell*, the *Caronia* court confirmed that the First Amendment protects truthful and non-misleading speech—regardless of whether that speech is off-label or relates to a commercial purpose.¹⁹⁶ The First Amendment analysis in *Caronia* also suggests that truthful, non-misleading speech, in and of itself, cannot be regulated in the absence of an accompanying unlawful act because the court construed the FDCA ‘as not criminalizing the simple promotion of a drug’s off-label use because such a construction would raise First Amendment concerns’.¹⁹⁷

Admittedly, not all legal commentators agree with the analyses of *Sorrell* and *Caronia*. Some academics have suggested that the *Caronia* court erred in applying heightened scrutiny and that the government could have made a stronger case that its regulatory framework satisfies the *Central Hudson* test.¹⁹⁸ Some commentators have even objected to the premise that off-label communications can be truthful; they argue that off-label communications may be considered ‘inherently misleading’.¹⁹⁹ The basis for this position appears to be an assumption that the ‘truth’ is unknowable until all of the manufacturer’s research has been evaluated, and until the off-label statement has been proven by substantial evidence; in other words, some commentators appear to believe that the truth of any statement related to an off-label use is ‘unknown’ because it may not be supported by the same level of evidence as claims that have already been approved by FDA.²⁰⁰ Despite these contentions, the argument that off-label communications are inherently misleading was rejected more than 15 years ago in the *WLF* cases.²⁰¹ The district court in *WLF* explained:

in asserting that any and all scientific claims about the safety, effectiveness, contraindications, side effects, and the like regarding prescription drugs are presumptively untruthful

¹⁹⁵ *Caronia*, 703 F.3d at 165.

¹⁹⁶ *Id.* at 164, 169.

¹⁹⁷ *Id.* at 160.

¹⁹⁸ See Greene, *supra* note 177, at 680, 683 (siding with the analysis of the *Caronia* dissent in arguing that heightened scrutiny was inappropriate and that FDA’s regulatory framework satisfies the *Central Hudson* test); Kesselheim & Mello, *supra* note 73, at 1584, 1597 (asserting that the government’s interest in ensuring the communication of accurate, unbiased communications to healthcare professionals should have been more of a focus of the *Central Hudson* analysis).

¹⁹⁹ See Greene, *supra* note 177, at 690, 692 (noting that in most pharmaceutical speech cases to date the government has not alleged the underlying speech which was false or misleading but asserting that the government should argue that statements about off-label uses are inherently misleading because they are not subject to verification); Stephanie M. Greene & Lars Noah, *Debate: Off-Label Drug Promotion and the First Amendment*, 162 U. PA. L. REV. 239, 243, 246 (2014) (asserting that off-label claims are not verifiable and that the truthfulness of off-label speech is ‘speculative, unknown, or inaccessible’); Christopher Robertson, *When Truth Cannot Be Presumed: The Regulation of Drug Promotion Under an Expanding First Amendment*, 94 B.U. L. REV. 545, 572–74 (2014) (challenging the presumption made by courts that off-label promotion is truthful and arguing that the burden of proving truthfulness for off-label claims should be placed on the drug manufacturer).

²⁰⁰ See Greene, Noah, *supra* note 199, at 246, 247 (Greene claiming that ‘the truth of off-label promotion cannot be presumed or proven without access to all of the manufacturer’s research’ and insisting that the FDA’s pre-approval requirement ensures that drugs are promoted based on ‘scientific proof’ and not ‘anecdotal information, conjecture, or profit motives’); Robertson, *supra* note 199, at 571–74 (arguing that the truth or falsity of off-label claims is unknown in part because the manufacturer ‘has declined the option of proving to FDA the efficacy and safety for the indication suggested’).

²⁰¹ See *WLF v Friedman*, 13 F. Supp. 2d 51, 68 (D.D.C. 1998).

or misleading until the FDA has had the opportunity to evaluate them, FDA exaggerates its overall place in the universe.²⁰²

Moreover, an oft-cited analysis of evidentiary support for off-label uses found that more than a quarter of the off-label uses studied ‘were supported by strong scientific evidence’.²⁰³ The ‘truth’ of an off-label communication lies not in whether the off-label use has been approved by FDA or in whether the off-label use is supported by substantial evidence, but in whether the communication accurately reflects all the available evidence.

Applying the logic of *Caronia* and *Sorrell*, any First Amendment-compliant regulatory framework should not restrict manufacturers from their right to engage in truthful and non-misleading dialog about the safety or efficacy of a drug, unless the framework is narrowly drawn to support a substantial government interest.²⁰⁴ This level of heightened scrutiny sets a very high bar for the government. Because as stated by the Supreme Court, if the government can achieve its interest without restricting speech, then it must do so.²⁰⁵ Essentially, restricting speech ‘must be a last—not first—resort’.²⁰⁶

Courts are more likely to uphold a regulatory scheme that allows for alternative means of communication.²⁰⁷ Accordingly, FDA may establish reasonable restrictions for well-defined, limited categories of speech, so long as meaningful, alternative avenues of communication are open. However, FDA’s current regulatory framework does not impose reasonable restrictions on certain well-defined types of communication; rather, despite a handful of FDA guidance documents that very narrowly authorize certain categories of manufacturer communications (e.g., distribution of reprints) in very limited circumstances under FDA’s exercise of enforcement discretion,²⁰⁸ FDA broadly prohibits nearly all communications by manufacturers regarding off-label uses. Such a broad, content- and speaker-based prohibition on speech is presumptively unconstitutional.²⁰⁹

In light of these First Amendment considerations, the regulation of manufacturer speech under the New Model does not focus on suppressing information but instead ensures that manufacturers may provide patients and prescribers with truthful and non-misleading, up-to-date information about therapeutic options. Manufacturers can and should play a critical role in this process.

IV.C Establish Understandable and Translatable Rules

Although certain FDA guidance documents attempt to clarify FDA’s regulatory requirements for certain limited categories of communications, none of these materials provide any clear explanation regarding how FDA’s regulatory framework comports to

²⁰² *Id.*

²⁰³ Radley et al., *supra* note 164, at 1023.

²⁰⁴ See *Sorrell v. IMS Health Inc.*, 131 S. Ct. 2653, 2667–68 (2011).

²⁰⁵ *Thompson v. W. States Med. Ctr.*, 535 U.S. 357, 371 (2002) (‘[I]f the Government could achieve its interests in a manner that does not restrict speech, or that restricts less speech, the Government must do so.’).

²⁰⁶ *Id.* at 373.

²⁰⁷ See, e.g., 44 *Liquormart, Inc. v. Rhode Island*, 517 U.S. 484, 502 (1996) (commenting that in its decision in *Florida Bar v. Went For It, Inc.*, the Court ‘upheld a 30-day prohibition against a certain form of legal solicitation largely because it left so many channels of communication open to Florida lawyers’ (emphasis added)).

²⁰⁸ See *supra* part III.E.

²⁰⁹ See *Sorrell*, 131 S. Ct. at 2667.

the First Amendment, even though such an explanation is crucial to ensuring, consistent with the Supreme Court's *Fox II* decision, that FDA's regulatory framework is not enforced in an arbitrary or discriminatory manner that chills protected speech.²¹⁰ Additionally, FDA's guidance documents largely fail to provide any actual, discernible 'guidance' to industry or to healthcare professionals. For example, as discussed above,²¹¹ the recent Risk Information Draft Guidance purports to permit drug manufacturers to communicate new risk information about a drug that may not satisfy the Agency's substantial evidence regulation.²¹² Because FDA does not even acknowledge that its non-binding guidance is intended to overrule a binding regulation, much less explain how this sort of rulemaking is legally permissible, drug manufacturers cannot be certain that FDA will not allege a violation of the substantial evidence regulation even if they comply with all the terms of the Risk Information Draft Guidance.

Essentially, unless FDA has specifically authorized a particular type of communication (e.g., dissemination of reprints) and issued specific, precise guidance, manufacturers cannot be sure whether or not the Agency considers the communication to be impermissible off-label promotion. Such vagueness may not comport with the due process clause requirement that laws 'must give fair notice of conduct that is forbidden or required', as recently reiterated by the Supreme Court in *Fox II*.²¹³ Given FDA's expansive view of what constitutes labeling and what evidence may support a new intended use for a drug,²¹⁴ almost any utterance by an employee or agent of the manufacturer in any context could run afoul of FDA's promotional rules. While FDA guidance documents have described several extra regulatory 'safe harbors' for certain manufacturer communications on the basis of enforcement discretion,²¹⁵ for the most part drug company speakers and their agents must tread at their own peril when not speaking within the four corners of the FDA-approved label. This vagueness in FDA's regulatory framework, especially with respect to what communications qualify as permissible 'scientific exchange', results in a chilling effect among manufacturers.

Accordingly, the New Model aims to be understandable by all stakeholders in a way that is actionable and translatable to the benefit of the public health.

IV.D Maintain the 'Gold Standard' FDA Approval Process While Permitting Truthful, Non-Misleading Claims

FDA frequently holds up the Agency's drug review process as the worldwide 'gold standard' for drug approval.²¹⁶ FDA will only approve a drug on the basis of substantial evidence of effectiveness—generally two adequate and well-controlled clinical

²¹⁰ See *Fox II*, 132 S. Ct. 2307, 2317 (2012).

²¹¹ See *supra* text accompanying notes 144–47.

²¹² See Risk Information Draft Guidance, *supra* note 144, at 6, 7; 21 C.F.R. § 202.1(e)(6).

²¹³ *Fox II*, 132 S. Ct. at 2317; see also *Connally v. General Constr. Co.*, 269 U.S. 385, 391 (1926) ('[A] statute which either forbids or requires the doing of an act in terms so vague that men of common intelligence must necessarily guess at its meaning and differ as to its application, violates the first essential of due process of law.').

²¹⁴ See *supra* part III.A–B.

²¹⁵ See *supra* part III.E.

²¹⁶ See, e.g., FDA, *FY 2012 Innovative Drug Approvals: Bringing Life Saving Drugs to Patients Quickly and Efficiently*, Dec. 2012, at 21, <http://www.fda.gov/downloads/aboutfda/reportsmanualsforms/reports/ucm330859.pdf> (accessed Apr. 10, 2015).

studies.²¹⁷ Because the standard of replication of adequate and well-controlled clinical studies is the most rigorous way to develop persuasive evidence that a product is likely to be effective, this drug approval standard should be maintained in the interest of the public health.²¹⁸

While the substantial evidence standard makes sense in the context of FDA review and approval decisions, requiring this same level of evidence to substantiate *any* claim or communication about a drug, as FDA regulations currently mandate but which is not required by the FDCA, fails to recognize that other valid sources of data and information can be used to support product claims. Healthcare professionals, formulary committees, and payors frequently rely upon evidence other than adequate and well-controlled studies to make informed decisions about the proper uses of a product. For example, claims based on economic modeling, government or third-party treatment guidelines, and patient case studies may offer valuable safety and efficacy information that would benefit patients, yet such claims would not amount to substantial evidence under FDA's current regime. Additionally, observational research has become increasingly reliable and robust, due to remarkable technological advances in data analysis, recording, and storage.²¹⁹

Therefore, the New Model should protect the integrity of the FDA approval process by maintaining the substantial evidence standard in the context of the approval of new drug applications and supplemental new drug applications, but it should also permit truthful and non-misleading claims about a drug based on 'competent and reliable scientific evidence'—the substantiation standard employed by the Federal Trade Commission ('FTC')²²⁰—that may not rise to the level of substantial evidence. Competent and reliable scientific evidence has been defined as

tests, analyses, research, studies, or other evidence based upon the expertise of professionals in the relevant area, that has been conducted and evaluated in an objective manner by persons qualified to do so, using procedures generally accepted in the profession to yield accurate and reliable results.²²¹

²¹⁷ 21 U.S.C. § 355(d).

²¹⁸ For example, a former director of the FDA's Center for Drug Evaluation and Research ('CDER') explained: '[B]efore the 1962 amendments to the [FDCA], controlled trials were still developing, and many marketed drugs were ineffective for their labeled uses. Now, the standard for evidence is the well-controlled study...'. Michelle Meadows, *Promoting Safe and Effective Drugs for 100 Years*, FDA CONSUMER MAGAZINE Jan. and Feb. 2006, <http://www.fda.gov/AboutFDA/WhatWeDo/History/ProductRegulation/PromotingSafeandEffectiveDrugsfor100Years/> (accessed Apr. 10, 2015). Similarly, commentators have agreed that '[t]he properly conducted [randomized controlled trial] permits an accurate, objective, and scientific assessment of whether a treatment works—and if so, how effective it is'. Jennifer Kulynych, *Will FDA Relinquish the 'Gold Standard' for New Drug Approval? Redefining "Substantial Evidence" in the FDA Modernization Act of 1997*, 54 FOOD & DRUG L.J. 127, 131 (1999).

²¹⁹ See, e.g., Andrew Grove, *Rethinking Clinical Trials*, 33 Science 1679, 1679 (2011); Barbara J. Evans, *Seven Pillars of A New Evidentiary Paradigm: The Food, Drug, and Cosmetic Act Enters the Genomic Era*, 85 NOTRE DAME L. REV. 419, 438–39 (2010).

²²⁰ See FTC, *Dietary Supplements: An Advertising Guide for Industry*, Apr. 2001, at 9, <http://www.business.ftc.gov/sites/default/files/pdf/bus09-dietary-supplements-advertising-guide-industry.pdf> (accessed Apr. 10, 2015).

²²¹ *Id.*

This standard would permit flexibility by potentially enabling myriad sources of relevant evidence, taking into account considerations of the relevant scientific community, to constitute adequate substantiation for drug claims.

IV.E Promote Development of New Uses and Maintain Appropriate Incentives to Entry

Criticism that a more permissive framework for the communication of product information would discourage the development of new uses for approved products must be taken seriously and addressed.²²² The underlying assumption of this criticism is that a more permissive framework would encourage sponsors to seek narrow uses to bring a product to market and then disseminate data on unapproved uses instead of seeking FDA approval for those uses.²²³ There are several market-driven and legal reasons that make this outcome less likely. First, in the post-healthcare reform era of evidenced-based medicine where the need to demonstrate value and cost-effectiveness to payors and healthcare professionals is as great as it has ever been, an off-label use of a product with limited safety and efficacy data is unlikely to gain significant market acceptance. Moreover, sponsors would likely be hesitant to rely on less than substantial evidence to fuel growth in commercially important uses given the product liability risks that such a marketing strategy would entail. Similar liability concerns would likely dissuade healthcare professionals from rapid adoption of unproven uses of drugs.

Notwithstanding these protective, market-driven forces, there are relatively modest legislative incentives that could be enacted to fully address the theoretical problem of manufacturers not seeking FDA approval for new uses. As evidenced by the success of the pediatric exclusivity program,²²⁴ similar incentives could be legislated to support the development and FDA approval of new uses if this theoretical problem materialized.²²⁵

²²² See, e.g., Brenda Sandburg, *Off-Label Ruling's Potential Fallout is 'Terrifying' FDA's Temple Says*, THE PINK SHEET, Dec. 17, 2012.

²²³ In light of *Caronia*, some commentators have noted a similar potential concern. See Kesselheim & Mello, *supra* note 73, at 1585. Specifically, Kesselheim and Mello observe that manufacturers, relying on *Caronia*, might be motivated to conduct 'poor-quality studies' to establish some minimum utility for an off-label use and then disseminate the study results in marketing communications. *Id.* To prevent such practices, the government can argue such communications are false and misleading if they fail to disclose relevant limitations, such as the results of other studies with contradictory results and the weaknesses of the study design. See *id.* at 1581–83.

²²⁴ See 21 U.S.C. § 355a (providing for an additional six months of market exclusivity for certain new drug applications if the drug manufacturer completes certain FDA-requested studies and submits information relating to the use of the drug in a pediatric population).

²²⁵ Under existing law, manufacturers that conduct new clinical investigations to support FDA approval for a new use (e.g., indication, dosage form, route of administration, or dosage strength) of an already-approved drug are entitled to three years of data exclusivity for the new use, meaning that a generic manufacturer cannot rely on the new clinical data during this time period to gain FDA approval for the new use. See 21 U.S.C. § 355(c)(3)(E)(iv); 21 C.F.R. § 314.108(b)(5)(ii). However, this exclusivity does not prevent FDA from approving a generic drug for the previously-approved use during the three-year exclusivity period, meaning that this exclusivity does not prevent new generic drugs from entering the market altogether. Consequently, the current three-year exclusivity may not sufficiently incentivize manufacturers to pursue supplemental FDA approval for all new uses.

The FDA approval process not only safeguards the public health by setting a high bar to minimize the possibility that approved uses will turn out to be unsafe or ineffective, but it can also promote higher quality information about drugs, as well as innovation,²²⁶ so long as a careful balance is maintained in terms of the standards for information exchange. The FDA approval process assesses, among other things, the limitations and potential biases in the clinical data for a drug.²²⁷ In that way, FDA approval requirements are intended to encourage the development of scientific knowledge.²²⁸ Nonetheless, reliance on the suppression of speech as a means of creating the incentive for drug manufacturers to pursue FDA approval for off-label uses is problematic. Accordingly, the New Model seeks to balance information exchange with the need to maintain high regulatory approval standards while ensuring that incentives still exist for the development and approval of new uses for previously-approved drugs.

V. THE NEW MODEL

This part proposes a New Model for the regulation of drug promotion intended to achieve the objectives described in part IV. Legal commentators have previously suggested various modifications to FDA's regulatory framework and enforcement strategy that would address similar policy and constitutional objectives. These recommendations have included, among others: expanding the use of 'safe harbors' to permit certain off-label communications,²²⁹ requiring drug manufacturers to bear the burden of establishing the truthfulness of off-label communications in any enforcement proceeding,²³⁰ permitting drug manufacturers to communicate off-label information—whether solicited or unsolicited—under certain circumstances depending on the strength of the information and the sophistication of the audience while imposing additional training, monitoring, reporting, and auditing requirements on manufacturers,²³¹ and requiring manufacturers to submit a supplemental new drug application for any particular off-label use that exceeds a specified percentage of the total prescriptions for the drug or a specified dollar amount of total sales of the drug.²³²

As an attempt at a more comprehensive proposal, our New Model would create a three-tiered regulatory framework corresponding to three different categories of

²²⁶ See Daniel Carpenter, Justin Grimmer & Eric Lomazoff, *Approval Regulation and Endogenous Consumer Confidence: Theories and Analogies to Licensing, Safety, and Financial Regulation*, 2010 REG. & GOVERNANCE 383, 398 (2010) (arguing that FDA regulation enhances innovation by contributing to better quality products).

²²⁷ See Kesselheim & Mello, *supra* note 73, at 1588 (nothing that FDA's scientists analyze all the information about a drug, independently verify the drug manufacturer's analyses, and scrutinize when the design of clinical studies).

²²⁸ See Robertson, *supra* note 199, at 565, n.110 (discussing the 'epistemic and economic motive for the FDCA', which ties 'investments to market rewards'); Eisenberg, *supra* note 178, at 347 (explaining that drug regulation promotes 'the development of credible information about the effects of drugs').

²²⁹ See Kesselheim & Mello, *supra* note 73, at 1597–1603 (discussing use of the 'substantial evidence' and 'substantial clinical experience' standards as potential evidentiary bases for permissible off-label communications and specifically suggesting that high-quality observational studies should qualify as substantial evidence).

²³⁰ See Robertson, *supra* note 199, at 571–74 (suggesting that FDA's regulatory framework can be reconfigured to comport with the First Amendment by focusing on the false and misleading aspects of off-label communications and by requiring manufacturers to establish truth as an affirmative defense).

²³¹ Bagley et al., *supra* note 67, at 385–91 (explaining that the proposal 'strongly affirms a company's right to distribute truthful and non-misleading off-label information to the marketplace when the benefits of that information for a given class of listener outweighs the risk of harm to the patient').

²³² *Id.* at 385.

manufacturer communications: (1) Scientific Exchange and Other Exempt Communications, (2) Non-Core Communications, and (3) Core Communications. The New Model is premised on the idea that FDA may, consistent with the First Amendment, set reasonable limits on well-defined categories of speech, provided that meaningful, alternative avenues of communication remain open. The level of regulation provided FDA for each category under the New Model is associated with the strength of the government's interest in regulating the specific communications included within each category and the immediacy of the commercial transaction being proposed.

As discussed further below, Scientific Exchange and Other Exempt Communications would include those communications either intended to advance the scientific enterprise²³³ or that otherwise do not qualify as labeling or advertising and that do not propose an immediate commercial transaction of the drug. The New Model would clarify that FDA has no authority to regulate Scientific Exchange and Other Exempt Communications. Non-Core Communications would include those communications that present truthful and non-misleading scientific information and that, due to the context of the communications and the entities involved, only tangentially relate to an immediate commercial transaction. The primary function of this communications category is to inform. FDA would have the authority to regulate such communications under a 'false and misleading' standard, but FDA would not be able to consider Non-Core Communications as evidence of a new intended use by the manufacturer. Lastly, Core Communications would include those communications, such as product package inserts, that directly propose an immediate commercial transaction and that are considered labeling. FDA would retain its full authority to require that all Core Communications be consistent with FDA-approved labeling and be supported by substantial evidence.

This New Model could largely be implemented through FDA's regulatory process (e.g., rulemakings to clarify the definition of 'scientific exchange' and the applicability of the intended use regulation and substantial evidence requirements), although certain legislative changes would likely be required.

V.A Scientific Exchange and Other Exempt Communications – FDA Would Have No Authority

Under the New Model, communications and materials that qualify as Scientific Exchange and Other Exempt Communications would be outside the scope of FDA's jurisdiction.²³⁴ Although existing FDA regulations state that FDA does not intend to restrict full access to the 'full exchange of scientific information', FDA has never spoken on the

²³³ The scientific method is defined as 'principles and procedures for the systematic pursuit of knowledge involving the recognition and formulation of a problem, the collection of data through observation and experiment, and the formulation and testing of hypotheses'. Merriam-Webster.com, *Scientific Method Definition*, <http://www.merriam-webster.com/dictionary/scientific%20method> (accessed Apr. 10, 2015). Under the New Model, where a communication is about such systematic pursuit of knowledge, then it would qualify as Scientific Exchange. The purpose is not merely to communicate but to communicate to advance the scientific enterprise.

²³⁴ 21 C.F.R. § 312.7(a).

full scope and applicability of this valuable ‘exchange’ to drug manufacturer communications, including, for instance, communications about a drug that is not the subject of an investigational new drug application. FDA’s limited statements on the subject include one regulatory preamble from over 25 years ago in which the Agency noted:

FDA’s understanding of commercial promotion does not place limits on the free exchange of scientific information (e.g., publishing results of scientific studies, letters to the editor in defense of public challenges, investigator conferences). However, responses by sponsors or investigators to unsolicited media inquiries or statements made in the exchange of scientific information should (1) make clear that the drug is investigational; (2) make no claims that the drug has been proven to be safe or effective; and (3) be truthful and non-misleading when measured against available information on the drug—and fairly represent available information. ...²³⁵

To allow manufacturers to engage in this important form of communication, without incurring the risk of enforcement actions or criminal prosecutions, the FDA must clarify the term ‘scientific exchange’ and build upon its limited prior statements. The New Model, therefore, more clearly defines Scientific Exchange and sets forth the category of materials that qualify as such. The New Model would also define a related category of ‘Other Exempt Communications’ that fall outside the scope of FDA regulation because they do not qualify as labeling or advertising under the FDCA, even if they do not technically qualify as Scientific Exchange.

V.A.1 Defining Scientific Exchange and Other Exempt Communications

Under the New Model, Scientific Exchange includes communications that advance the scientific enterprise and do not primarily promote the sale of any particular drug for any particular use. The four essential requirements for Scientific Exchange are as follows:

1. Scientific Exchange involves interactions that advance the systematic pursuit of knowledge among only sophisticated, highly educated, and experienced entities, such as biopharmaceutical companies, scientific researchers, healthcare professionals, formulary committees, and payors.
2. The information disseminated is factual, scientific, and data-driven.
3. The information disseminated is placed in the appropriate context (e.g., trial design limitations and potential biases are disclosed), so that the audience may evaluate the proper weight to afford such data.²³⁶
4. The information does not include conclusions or promotional claims about the safety or effectiveness of a drug for a particular use.

²³⁵ 52 Fed. Reg. 19,466, 19,475 (May 22, 1987).

²³⁶ See Pharmaceutical Research and Manufacturers of America (‘PhRMA’), *Comments re: Communications and Activities Related to Off-Label Uses of Marketed Products and Use of Products Not Yet Legally Marketed*, Docket No. FDA-2011-N-0912, Mar. 27, 2012 at 13, <http://www.regulations.gov/#!documentDetail;D=FDA-2011-N-0912-0018> (accessed Apr. 10, 2015).

Examples of Scientific Exchange include, among others:

- presentations, speeches, abstracts, and other information disseminated during meetings or conferences sponsored by healthcare professionals, medical associations, or scientific research organizations;²³⁷
- dissemination of scientifically rigorous, peer-reviewed publications in scientific and medical journals, regardless of whether or not such publications address adequate, well-controlled studies, provided that limitations of the data relied on in such publications are appropriately disclosed,²³⁸ and provided that the publications comply with internationally-recognized guidelines on authorship and the disclosure of conflicts of interest;²³⁹
- dissemination of peer-reviewed scientific or medical reference textbooks;²⁴⁰
- dissemination of scientifically rigorous CPGs developed by governmental bodies, medical organizations, non-profit organizations, or other third parties;²⁴¹
- direct communications among scientific and medical researchers regarding research studies and a manufacturer's product pipeline;²⁴² and
- rebuttals of erroneous or incomplete scientific information about a drug, which may include responses to CER findings presented by academic detailers.²⁴³

Besides Scientific Exchange, there are Other Exempt Communications that fall outside the scope of FDA regulation because FDA has no statutory authority to regulate them. As discussed in parts III.A–B, *supra*, FDA's authority does not extend to all forms of 'promotion'. Rather, FDA only has the authority to regulate 'labeling' and 'advertising' (although oral statements may fall within the scope of the intended use regulation and are indirectly subject to FDA regulation). Other Exempt Communications are those communications, other than Scientific Exchange, that do not qualify as labeling or advertising.

Examples of Other Exempt Communications include, among others:

- communications specifically directed toward investors, rather than the general public, such as annual reports or other securities filings, that may reference the results of clinical research, a regulatory event (e.g., submission or approval of

²³⁷ See *id.* at 14.

²³⁸ *Id.*; see also Revised Draft Reprints Guidance, *supra* note 137, at 7–10.

²³⁹ See International Committee of Medical Journal Editors, *Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals*, Dec. 2014, at 2–4, <http://www.icmje.org/about-icmje/faqs/icmje-recommendations/> (accessed Apr. 10, 2015).

²⁴⁰ See Revised Draft Reprints Guidance, *supra* note 137, at 10–14.

²⁴¹ See *id.* at 14–17; PhRMA, *Comments re: Communications and Activities Related to Off-Label Uses of Marketed Products and Use of Products Not Yet Legally Marketed*, Docket No. FDA-2011-N-0912, Mar. 27, 2012, at 14–15, <http://www.regulations.gov/#!documentDetail;D=FDA-2011-N-0912-0018> (accessed Apr. 10, 2015).

²⁴² See *id.* at 14.

²⁴³ See *supra* text accompanying notes 182–87. The current regulatory framework, which does not clearly permit such rebuttals by manufacturers, is inconsistent with the principles of *Sorrell*, which calls for speaker- and content-neutrality for any restriction on speech. See *Sorrell v. IMS Health Inc.*, 131 S. Ct. 2653, 2660 (2011).

- a new drug application), or other product-specific information material to a drug manufacturer's shareholders;²⁴⁴ and
- industry-supported, independent,²⁴⁵ and accredited CME programs intended to educate physicians but that may not directly advance the scientific enterprise and therefore may not qualify as scientific exchange.²⁴⁶

V.A.2 FDA's Proposed Authority over Scientific Exchange and Other Exempt Communications

In contrast to product labeling, detailing materials, and oral communications by sales representatives, Scientific Exchange and Other Exempt Communications cover manufacturers' communications that do not directly prescribe, recommend, or suggest a use related to any commercial transaction. Hence, Scientific Exchange and other Exempt Communications are not purely commercial speech under the First Amendment because Scientific Exchange and Other Exempt Communications do not directly 'propose' a commercial transaction.²⁴⁷ The government's interest in regulating the non-commercial aspects of Scientific Exchange (i.e., the scientific expression itself) is far less significant than the government's interest in regulating commercial speech.²⁴⁸

²⁴⁴ Certainly, investor-directed communications should be truthful and non-misleading, but the regulation of such communications should generally be a matter for the Securities and Exchange Commission ('SEC'), rather than FDA. Investor-directed communications would *not* be exempt from FDA regulation if a drug manufacturer repurposed such communications for use in drug promotion to healthcare professionals or the general public, such as by having sales representatives share with physicians securities filings that discuss the manufacturer's drug.

²⁴⁵ As per FDA's CME Guidance, an industry-supported CME program is nonetheless 'independent' from the substantive influence of a manufacturer if, among other things, the manufacturer has no direct or indirect role in determining the content of the program or selecting the speakers. See CME Guidance, *supra* note 37, at 64095, 64097.

²⁴⁶ Industry has previously argued that such independent CME programs should be considered Scientific Exchange and therefore exempt from FDA regulation. See, e.g., Biotechnology Industry Organization, *Comments re: Communications and Activities Related to Off-Label Uses of Marketed Products and Use of Products Not Yet Legally Marketed*, Docket No. FDA-2011-N-0912, Mar. 27, 2012, at 7, <http://www.regulations.gov/#!documentDetail;D=FDA-2011-N-0912-0014> (accessed Apr. 10, 2015). Whether or not such CME programs directly fall under the umbrella of Scientific Exchange, they are exempt from FDA regulation because they do not qualify as labeling (or advertising for that matter) in that the manufacturer has no control over the content of an independent CME program; a CME program is not intended for use in the sale and distribution of the drug, and a CME program is not an 'essential supplement' to the drug label. See *Kordel v. United States*, 335 U.S. 345, 348, 350 (1948). FDA's existing CME Guidance even appears to acknowledge as much. CME Guidance, *supra* note 37, at 64094 ('[CME] programs and materials performed and disseminated by companies are subject to the labeling and advertising provisions of the [FDCA], whereas the truly independent and non-promotional industry-supported activities have not been subject to FDA regulation.').

²⁴⁷ See *Bolger v. Youngs Drug Prods. Corp.*, 463 U.S. 60, 66 (1983); *Central Hudson Gas & Elec. Corp. v. Public Serv. Comm'n*, 447 U.S. 557, 561 (1980). But see *WLF I*, 13 F. Supp. 2d 51, 64 (D.D.C. 1998) ('[T]here can be little question that the reason that drug manufacturers wish to disseminate enduring materials and sponsor CME seminars is because they believe that such activity will increase the sales volume of their drugs.').

²⁴⁸ See, e.g., *WLF I*, 13 F. Supp. 2d at 62 ('It is beyond dispute that when considered outside of the context of manufacturer promotion of their drug products, CME seminars, peer-reviewed medical journal articles and commercially-available medical textbooks merit the highest degree of constitutional protection. Scientific and academic speech reside at the core of the First Amendment.'). *Bd. of Trs. of Leland Stanford Jr. Univ. v. Sullivan*, 773 F. Supp. 472, 474 (D.D.C. 1991) ('[T]he First Amendment protects scientific expression and debate just as it protects political and artistic expression.').

Information that is exchanged in the interest of scientific discovery is at the heart of the protection provided by the First Amendment.²⁴⁹ Yet, FDA's current regulatory framework does not provide sufficient clarity to manufacturers that the types of Scientific Exchange listed above will not be considered unlawful by the Agency. Consequently, a chilling effect results, meaning that manufacturers may refrain from engaging in Scientific Exchange that would otherwise be beneficial to the public health by providing accurate, up-to-date medical information to support research and to guide patient care. Therefore, the New Model would make clear that FDA has no authority to regulate such Scientific Exchange, so that manufacturers would be assured that engaging in Scientific Exchange would not run afoul of the FDCA and FDA regulations.

With respect to Other Exempt Communications, FDA currently has no authority to regulate them because they do not qualify as labeling or advertising. The New Model would therefore maintain the status quo with respect to this category of communications.

V.B. Non-Core Communications—FDA Would Apply Only a 'False and Misleading' Standard

Under FDA's current regulatory framework, a wide range of truthful and non-misleading manufacturer communications of important scientific information about a drug are prohibited or significantly restricted merely because the communications deviate from the FDA-approved labeling of the drug or are not supported by substantial evidence.²⁵⁰ FDA's current framework essentially only includes two categories of communications: (1) 'promotional' communications over which FDA asserts its full regulatory authority and (2) scientific exchange over which FDA has no regulatory authority.

As previously noted, not all manufacturer communications are designed to propose the immediate sale and distribution of a drug in interstate commerce. Rather, many manufacturer communications have a mix of both commercial and non-commercial aspects. The primary intent of these communications may be to educate healthcare professionals, payors, and formulary committees to inform treatment decisions (in the case of healthcare professionals) or coverage and reimbursement decisions (in the case of payors and formulary committees). Such Non-Core Communications are only indirectly related to a commercial transaction, so the justification for regulating Non-Core Communications in the same manner as traditional promotional communications and advertising is unconvincing.²⁵¹

Thus, not all communications should be considered 'promotional'. On the other hand, not all communications that do not propose the immediate sale of a drug are scientific exchange. The Non-Core communications category of the New Model would remove the chilling effect associated with certain types of communications, such as

²⁴⁹ Cf. *Ony, Inc. v. Cornerstone Therapeutics, Inc.*, 720 F.3d 490, 492, 496 (2d Cir. 2013) (recognizing that 'academic freedom is a special concern of the First Amendment' in holding that 'statements of scientific conclusions about unsettled matters of scientific debate cannot give rise to liability' for false advertising).

²⁵⁰ See *supra* part III.B–C; 21 C.F.R. § 202.1(6).

²⁵¹ Non-Core Communications, due to the setting and context of the communications, nonetheless may be considered more promotional and therefore more closely associated with a commercial transaction than Scientific Exchange communications. Hence, the justification for regulating Non-Core Communications is stronger than for Scientific Exchange.

manufacturer-sponsored speaker presentations by expert healthcare professionals to other healthcare professionals, that FDA might today view as evidence of a new intended use of a drug. At the same time, the Non-Core Communications category would alleviate the need for industry to argue that any non-promotional communication necessarily qualifies as Scientific Exchange. In other words, some communications like speaker presentations that manufacturers previously might have argued fell under the umbrella of Scientific Exchange and were therefore exempt from FDA regulation would instead be subject to direct FDA regulation as Non-Core Communications.

Under the New Model, FDA would not have the authority to consider Non-Core Communications as evidence of a new intended use nor would FDA have the authority to require that Non-Core Communications be supported by substantial evidence. FDA would have the authority to regulate Non-Core Communications that are false or misleading. In determining whether a Non-Core Communication is false or misleading, FDA would rely on a more flexible substantiation standard than the current substantial evidence requirement.

V.B.1 Defining Non-Core Communications

Non-Core Communications include those written materials and oral statements that do not qualify as Core Communications, discussed *infra*, but that may still be considered to indirectly propose the sale and distribution of a drug. Their primary function is to inform. Examples of non-core communications include:

- *Speaker presentations to healthcare professionals.* Manufacturer-sponsored speaker programs recruit leading healthcare professionals to speak to other healthcare professionals in local communities about a particular drug.²⁵² This physician-to-physician communication is useful to help educate and inform the medical community about the benefits, risks, and appropriate uses of a drug.²⁵³ Admittedly, speaker presentations have been the subject of some government scrutiny and public controversy in recent years, as some pharmaceutical companies have allegedly used them to market their drugs improperly or to provide unlawful kickbacks to physician speakers.²⁵⁴ Nevertheless, properly-executed speaker presentations do have educational value because they tend to be highly data-driven and focus on detailed scientific information, such as the results of clinical trials of a drug. Their function is to raise awareness of a drug in the medical community and educate healthcare professionals who may otherwise lack enough information to know whether or not to prescribe the drug.

²⁵² See *United States v. Caronia*, 703 F.3d 149, 156 (2d Cir. 2012).

²⁵³ See PhRMA, *Code on Interactions With Healthcare Professionals*, 2008, at 9 ('PhRMA Code'), http://www.phrma.org/sites/default/files/pdf/phrma_marketing_code_2008.pdf (accessed Apr. 10, 2015).

²⁵⁴ See Charles Ornstein, Eric Sagara & Ryann G. Jones, *As Full Disclosure Nears, Doctors' Pay for Drug Talks Plummet*, PROPUBLICA, Mar. 3, 2014, <http://www.propublica.org/article/as-full-disclosure-nears-doctors-pay-for-drug-talks-plummet> (accessed Apr. 10, 2015). The controversy has led at least one pharmaceutical manufacturer to discontinue all payments to physicians for speaker presentations. See Sarah K. diFrancesca, *GSK Announcement May Change Industry Speaker Programs*, LAW360, Feb. 14, 2014, <http://www.law360.com/articles/505701/gsk-announcement-may-change-industry-speaker-programs> (accessed Apr. 10, 2015).

Moreover, pharmaceutical industry codes provide that legitimate speaker programs may not be intended as inducements or rewards for prescribing a particular drug.²⁵⁵ Nevertheless, manufacturer-sponsored speaker presentations, unlike industry-supported CME programs delivered by healthcare professionals, include conclusions and promotional claims about the safety and effectiveness of a drug for particular uses, so they are properly considered Non-Core Communications, rather than Scientific Exchange.

- *Discussions by 'MSLs' with healthcare professionals that do not make conclusions or promotional claims of safety or effectiveness.* Unlike sales representatives, MSLs are employed by drug companies to serve as scientific resources to the medical community and develop and maintain relationships with key opinion leaders.²⁵⁶ MSLs generally have advanced scientific degrees and training.²⁵⁷ MSLs' responsibilities include conveying complex medical and technical information to healthcare professionals, keeping abreast of relevant scientific developments, representing the manufacturer at scientific symposia and meetings, supporting clinical trials by identifying sites, educating investigators, and attending investigator meetings, and responding to unsolicited requests.²⁵⁸ MSLs' communications are not traditional sales and promotional activities like those of sales representatives. Because MSLs are communicating to an educated audience of healthcare professionals who have the expertise to evaluate the merits of the information presented, the New Model would permit an MSL to reactively and proactively communicate truthful, non-misleading information to healthcare professionals, even if such information relates to an off-label use or is not supported by substantial evidence, provided that the MSL does not make conclusions related to safety and effectiveness and provided that the MSL discloses the relevant limitations of the data.
- *Dissemination of HCEI and pipeline information to payors, formulary committees, and similar entities.*²⁵⁹ Payors and formulary committees evaluate HCEI, even where a drug is not yet approved for a particular indication, in making coverage and reimbursement decisions. Although the FDCA currently allows manufacturers to provide to 'a formulary committee, or other similar entity' HCEI that 'directly relates' to an *approved* indication if the information is based on 'competent and reliable scientific evidence', this provision does not permit the communication of HCEI about off-label uses nor does it permit communication

²⁵⁵ See PhRMA Code, at 9, http://www.phrma.org/sites/default/files/pdf/phrma_marketing_code_2008.pdf (accessed Apr. 10, 2015).

²⁵⁶ See Medical Science Liaison Society, *What Is a Medical Science Liaison?*, <http://www.themsls.org/what-is-an-msl/> (accessed Apr. 10, 2015).

²⁵⁷ *Id.*

²⁵⁸ An FDA draft guidance currently authorizes MSLs to respond to unsolicited requests from healthcare professionals but only under limited circumstances and in a very restrictive manner prescribed by the draft guidance. See generally Unsolicited Requests Draft Guidance, *supra* note 140.

²⁵⁹ Although FDA's current authority to regulate these payor communications as labeling is somewhat questionable, such payor communications ideally fall under the Non-Core Communications category of the New Model because their primary intent is to inform, rather than directly promote the immediate sale of a drug. To the extent necessary, modest legislative changes could be adopted to clarify that HCEI and pipeline information disseminated to payors and formulary committees constitutes labeling and is subject only to a false and misleading standard.

of HCEI to healthcare professionals.²⁶⁰ Manufacturers should be permitted to communicate HCEI about unapproved, investigational products to payors, formulary committees, and compendia publishers to facilitate this decision-making and ensure that patients will have access to reimbursement for a drug upon its approval. Such communications do not propose an immediate commercial transaction because payors, formulary committees, and related entities do not directly purchase or prescribe a drug.

- *Manufacturer-sponsored scientific symposia that are primarily intended to educate physicians but that do not satisfy the criteria of FDA's CME Guidance.*²⁶¹ FDA's existing CME Guidance outlines numerous criteria for differentiating between industry-supported CME programs that are independent of a manufacturer's influence and which are not subject to FDA regulation, and those that are influenced by the manufacturer and which FDA insists should be subject to the full gamut of FDA regulation.²⁶² Because of FDA's longstanding position, manufacturers have generally refrained from sponsoring and hosting their own scientific symposia and educational programs to discuss the latest clinical research regarding a drug or other clinical developments out of fear that such programs will be viewed as creating a new, off-label intended use. Such manufacturer-sponsored symposia would not be discouraged in this manner under the New Model. Despite their lack of 'independence', they can still serve a valuable educational function, provided of course that the information communicated by the manufacturer is truthful and non-misleading and includes appropriate disclosures.

V.B.2 FDA's Proposed Authority over Non-Core Communications

For all Non-Core Communications, FDA's authority would be limited to the prohibition of false and misleading speech because such communications do not propose a direct, immediate commercial transaction, so the government's interest in regulating these communications is relatively weak. FDA would not have the authority under the New Model to rely on Non-Core Communications as evidence that a manufacturer intended a new, unapproved use for a drug nor would FDA be able to require substantial evidence to substantiate all promotional claims of safety or effectiveness in Non-Core Communications. Consistent with the First Amendment principles espoused in *Sorrell* and *Caronia*, FDA would not be able to construe a manufacturer's truthful and non-misleading speech about the *lawful* use of a drug (i.e., off-label prescribing) as *unlawful* activity (i.e., introducing an unapproved or misbranded drug into interstate commerce).

Also consistent with the First Amendment, FDA would retain the authority to prohibit all false and misleading Non-Core Communications because false and misleading speech warrants no constitutional protection.²⁶³ However, the New Model would not deem communications to be false and misleading simply because they are not

²⁶⁰ See 21 U.S.C. § 352(a).

²⁶¹ See generally CME Guidance, *supra* note 37.

²⁶² See *id.* at 64095.

²⁶³ See, e.g., *United States v. Caronia*, 703 F.3d 149, 164 (2d Cir. 2012).

supported by two adequate and well-controlled studies. Rather, the New Model would consider Non-Core Communications to be false and misleading if they are not supported by competent and reliable scientific evidence.²⁶⁴ This standard would permit flexibility by allowing a wide range of relevant evidence to be considered in determining whether a statement is adequately substantiated, taking into account the level of substantiation that experts in the field believe is reasonable. It would not strictly require two adequate, well-controlled studies to support all efficacy and safety claims.

Applying this substantiation standard to Non-Core communications would still limit the ability of manufacturers to disseminate false and misleading product information while also providing healthcare professionals, payors, and other audiences the benefit of access to up-to-date information about a drug. Furthermore, the likelihood that information conveyed via Non-Core Communications would ‘mislead’ the audience is low given that Non-Core Communications are primarily intended for learned, sophisticated audiences like healthcare professionals, payors, and formulary committees. Recognizing the ability of these audiences to evaluate critically the merit of scientific and medical information, the Supreme Court has rejected the paternalistic notion that healthcare professionals might make ‘bad decisions’ (e.g., prescribe unnecessary medications) when presented with truthful, factual information about drugs.²⁶⁵ By limiting FDA’s regulatory authority over Non-Core Communications and adopting a more flexible substantiation standard for claims made in Non-Core Communications, the New Model would impose a less paternalistic regulatory framework than the existing regime. The New Model would increase access to product information while ensuring that such information is based on data that can be replicated and validated by others in the relevant scientific community.

V.C Core Communications – FDA’s Existing Regulatory Framework Would Apply
Core Communications would include those communications, such as product package inserts, that directly propose a commercial transaction and that are properly considered ‘labeling’ under the FDCA (i.e., materials that are part of an integrated distribution program and serve as essential supplements to the drug label, even if not shipped directly with the drug²⁶⁶). The government’s interest in restricting drug manufacturer speech is at its strongest when restricting such promotional communications that are directed toward the sale and distribution of a drug. FDA would retain its existing authority to require that all Core Communications be consistent with the FDA-approved labeling for the drug and be supported by substantial evidence. The New Model’s restrictions on Core Communications should nonetheless comport with the First Amendment because of the alternative, less restrictive avenues of communication also provided by the New Model with regard to Scientific Exchange and Non-Core Communications.

²⁶⁴ See FTC, *Dietary Supplements: An Advertising Guide for Industry*, Apr. 2001, at 9, <http://www.business.ftc.gov/sites/default/files/pdf/bus09-dietary-supplements-advertising-guide-industry.pdf> (accessed Apr. 10, 2015).

²⁶⁵ *Thompson v. W. States Med. Ctr.*, 535 U.S. 357, 374 (2002); see also *Sorrell v. IMS Health Inc.*, 131 S. Ct. 2653, 2671 (2011).

²⁶⁶ See *Kordel v. United States*, 335 U.S. 345, 348–50 (1948).

V.C.1 Defining Core Communications

Core Communications include only those written materials that are specifically designed to promote an immediate commercial transaction involving the drug. Examples of Core Communications include:

- the FDA-approved label and package insert for the drug,
- sales aids presented to healthcare professionals,
- product-specific websites intended for healthcare professionals and patients,
- direct-to-consumer advertisements, and
- other written materials developed by the manufacturer that describe the drug and are part of an immediate commercial transaction involving the drug, such as promotional brochures provided to healthcare professionals.

Each of these communications is ‘interdependent’ with the drug itself, as described in *Kordel*.²⁶⁷ They describe the uses of the drug in the context of an immediate commercial transaction: the purchase (or more accurately, the prescribing) of a drug offered for sale in interstate commerce. Core Communications do not encompass every statement that could possibly, at some point in the future, have some bearing on a healthcare professional’s decision to prescribe a drug. Rather, Core Communications are limited to those communications primarily intended to propose an immediate commercial transaction.

V.C.2 FDA’s Proposed Authority over Core Communications

The New Model would apply FDA’s existing regulatory framework to Core Communications. In other words, FDA could consider Core Communications as evidence that a drug is intended for an unapproved new use and could determine that Core Communications are false and misleading because they are not supported by substantial evidence. The logic of FDA’s existing regulations describing intended uses²⁶⁸ and substantial evidence²⁶⁹ would remain in effect, but their reach would be limited only to Core Communications and not Non-Core Communications or Scientific Exchange. Hence, all Core Communications would need to be consistent with the FDA-approved labeling for the drug, and claims of safety and effectiveness would generally need to be substantiated by two adequate, well-controlled studies. Additionally, oral statements about Core Communications, such as a sales representative’s description of the package insert or a sales representative’s presentation of a sales aid to a healthcare professional, could be used as evidence of intended use.

Even though the New Model would limit the dissemination of off-label information in Core Communications, this restriction should not run afoul of the First Amendment for two reasons. First, it is necessary to advance the government’s interest in protecting the FDA approval process and ensuring that manufacturers cannot advertise and promote a drug in a commercial context for an unapproved use. Second, the restriction only applies to Core Communications, leaving manufacturers free to share truthful and non-misleading information about off-label uses in Non-Core Communications

²⁶⁷ See *id.*

²⁶⁸ See 21 C.F.R. § 201.128.

²⁶⁹ See 21 C.F.R. §§ 201.57(c)(2)(iii)-(v); 202.1(e)(6).

and Scientific Exchange and Other Exempt Communications. By leaving open alternative channels of communication, the New Model protects manufacturers' First Amendment interests.²⁷⁰

VI. CONCLUSION

FDA's current regulatory framework for drug promotion, by significantly restricting the ability of drug manufacturers to communicate important, accurate, up-to-date scientific information about their products that is truthful and non-misleading, runs afoul of the First Amendment and actually runs counter to the Agency's public health mission. Industry stakeholders have long been urging FDA to announce clearer, more flexible rules that respect manufacturers' First Amendment rights. Yet, FDA's limited actions to date—the release of several non-binding guidance documents on particular topic areas—fail to provide the pharmaceutical industry with the clarity it is seeking and also fail to elucidate how the Agency's regulatory framework comports with the First Amendment.

The New Model described in this article represents an initial proposal for a modern, sustainable regulatory framework that comprehensively addresses drug promotion while protecting the public health, protecting manufacturers' First Amendment rights, establishing clear and understandable rules, and maintaining the integrity of the FDA approval process. We believe that healthcare professionals and patients, in addition to drug manufacturers, would benefit from the implementation of the New Model. We hope that the New Model can be used as a framework to guide discussions between industry, FDA, and Congress regarding the future of the regulation of drug promotion.

²⁷⁰ See, e.g., 44 *Liquormart, Inc. v. Rhode Island*, 517 U.S. 484, 502 (1996); *Florida Bar v. Went For It, Inc.*, 515 U.S. 618, 633–34 (1995).