FDA, Medical Communications, and Intended Use—A New Challenge to First and Fifth Amendment Constraints on Government Power

COLEEN KLASMEIER*

ABSTRACT

This Article aims to fill a gap in the scholarly literature relating to the federal government's regulation of drug and medical device manufacturers' speech regarding uses of their products that have not been approved by the U.S. Food and Drug Administration (FDA). Academics have noted the conflict between enforcement of the Federal Food, Drug, and Cosmetic Act (FDCA) against individuals and companies engaged in truthful, non-misleading communications about off-label uses, and First and Fifth Amendment prohibitions on ambiguous regulatory standards that govern speech. But there has been no comprehensive analysis of the complex web of policies that FDA has established over decades, purporting to grant "safe harbor" status to certain forms of manufacturer communications about off-label uses of medical products. Such an assessment is necessary because FDA has completed a rulemaking proceeding to amend the regulation defining intended use, a foundational concept that determines both whether a product is subject to regulation as a drug or device and the scope of a manufacturer's FDCA liability for off-label promotion. Under the regulatory amendments, FDA asserts, even accurate scientific speech about off-label uses can be used as evidence of intended use, and therefore can be the basis for enforcement under the FDCA. This Article provides a detailed account of FDA's creation and repeated modification of policies allowing off-label communications. The purpose of this account is to provide a resource that is not otherwise available in legal publications. It is also intended to call attention to the impact of the new definition of intended use on the safe harbors for manufacturers' medical communications and the associated constitutional issues.

I. INTRODUCTION

Under the Federal Food, Drug, and Cosmetic Act (FDCA), the U.S. Food and Drug Administration (FDA) regulates drugs and medical devices, requiring them to meet statutory and regulatory standards governing safety, effectiveness, manufacturing, and labeling. Central to the agency's mission is the review of medical products prior to marketing, based on extensive submissions of data and other information generated by the developers of those products to obtain licensure of the product under specified

* Head of Legal—Regulatory Affairs and Patient Safety (U.S.), Roche Diagnostics. This Article was written while the author was a partner and the Head of the Food, Drug, and Medical Device Regulatory practice at Sidley Austin LLP and co-counsel to the Medical Information Working Group (MIWG). The author would like to acknowledge the contributions of her former colleagues at Sidley and the conscientious cite-checking assistance provided by Hannah Leibson and Dani Elks.

conditions of use. Drugs and medical devices are commonly used for health conditions or by patient populations other than those for which FDA has granted marketing authorization and which therefore are not addressed in the official labeling—so-called "off-label" uses. In general, FDA does not directly regulate health care professionals' decisions to prescribe or use drugs and devices in ways that depart from the official labeling, but prevalent off-label use can invite scrutiny and ultimately result in significant liability on the part of the manufacturer. In particular, prosecutors may view off-label use as a sign that the manufacturer has taken steps to encourage that use as a way of expanding sales; that the manufacturer subjectively wanted or intended for its product to be used off-label; or that the manufacturer actively promoted off-label use through sales representatives' communications.

FDA's power to regulate manufacturer communications, including those respecting off-label use, is subject to constitutional limitations, as the courts have recognized. In invalidating a Vermont measure that burdened drug-related communications, the Supreme Court in the 2011 *Sorrell* decision affirmed that "[s]peech in aid of pharmaceutical marketing . . . is a form of expression protected by the Free Speech Clause of the First Amendment."[1] Even before *Sorrell*, however, FDA's regulation of manufacturer speech about drugs and medical devices was subject to scrutiny. Since *Virginia State Board of Pharmacy v. Virginia Citizens Consumer Council, Inc.*[2] was decided in 1976, it has been settled law that the government's regulation of accurate manufacturer speech about all uses of lawfully marketed drugs and medical devices is subject to constitutional limitation. Accordingly, in the last decade, federal courts have rejected government efforts to proscribe speech about off-label uses of neurology and cardiovascular drug products.[3]

FDA recognizes the public health importance of assuring that drug and medical device manufacturers have the ability to provide information about off-label uses of their products. Such information may be provided in accordance with various FDA "safe harbors." Set forth in informal statements, guidance documents, and regulations, the safe harbors describe the circumstances in which off-label communications are effectively insulated from regulation and enforcement. Safe harbors may also provide FDA's recommendations for the content and format of manufacturers' off label communications. Although the earliest of these policies predated even the decision in *Virginia Board*, FDA has been criticized for failing to take adequate account of the First Amendment in its approach to manufacturer speech about off-label uses. Manufacturers of drugs and medical devices have repeatedly asked FDA to adjust the safe harbors, requesting changes to more clearly permit accurate speech about off-label uses. They have also asked FDA to provide clear, *a priori* standards governing off-label communications, so that accurate off-label speech is not chilled.[4] In 2018,

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

2 425 U.S. 748 (1976).

3 United States v. Caronia, 703 F.3d 149 (2nd Cir. 2012); Amarin Pharma, Inc. v. FDA, 119 F. Supp. 3d 196 (S.D.N.Y. 2015).

4 *See, e.g.*, Citizen Petition of MIWG, Docket No. FDA-2013-P-0079 (Sept. 3, 2013), https://www.regulations.gov/document/FDA-2013-P-1079-0001; AdvaMed, Comment in response to Docket No. FDA-2015-N-2002, Proposed Rule on Clarification of When Products Made or Derived from Tobacco Are Regulated as Drugs, Devices, or Combination Products; Amendments to Regulations Regarding "Intended Uses" (Dec. 18, 2015), https://www.regulations.gov/comment/FDA-2015-N-2002-1721; Petition to Stay and for Reconsideration of MIWG, Docket No. FDA-2016-P-1149-0048 (Feb. 8, 2017), https://www.regulations.gov/document/FDA-2011-P-0512-0011; Statement of Michael Labson,

FDA responded to industry's requests by publishing two new guidance documents, providing recommendations to facilitate manufacturer communications about off-label uses to payors and addressing the circumstances in which manufacturers could, from FDA's perspective, communicate beyond the four corners of the official labeling.

Three years later, however, FDA took a major regulatory step that raised questions about the agency's commitment to the "safe harbors" and to constitutional limitations on FDA to regulate speech. On August 2, 2021, FDA published a final rule amending the definitions of "intended use" in two provisions of the Code of Federal Regulations—one for drugs, and the other for medical devices. As discussed further below, in issuing the final rule, FDA recognized the safe harbors, but also indicated that communications undertaken in reliance on those policies would not necessarily be insulated from enforcement or regulation. Beyond the preamble, the changes to the definitions themselves are significant, because they introduce new breadth into the codified language and give the government more latitude in enforcement actions aimed at manufacturers whose products have widespread off-label uses.

This Article describes FDA's regulation of manufacturer speech about off-label uses and analyzes the effects of the 2021 final rule and accompanying preamble on FDA's "safe harbor" policies, in light of their long history. Part II sets forth a detailed explication of the relevant provisions of the FDCA. It also recounts—for the first time—the entire sixty-plus-year history of FDA's effort to establish and refine a set of "safe harbor" policies permitting manufacturers to engage in off-label communications. Part III recounts the rulemaking proceeding, which culminated with the publication of the August 2, 2021, final rule amending the regulations defining intended use for drugs and medical devices. This part then describes the consequences of the amended regulations and the issues raised by FDA's approach. Part IV addresses proposals to realign FDA's approach with its public health objectives and the governing statutory provisions and constitutional limitations.

Covington & Burling, on behalf of Pharmaceutical Research and Manufacturers of America (PhRMA), FDA Public Hearing on Manufacturer Communications Regarding Unapproved Uses of Approved or Cleared Medical Products, at 29 (Nov. 9, 2016), https://www.regulations.gov/document/FDA-2016-N-1149-0008; Statement by Khatereh R. Calleja, Senior Vice Pres., Technology & Regulatory Affairs, on behalf of the Advanced Medical Technology Association (AdvaMed), *FDA Public Hearing on Manufacturer Communications Regarding Unapproved Uses of Approved or Cleared Medical Products*, at 53 (Nov. 9, 2016), https://www.regulations.gov/document/FDA-2016-N-1149-0008. FDA sought comment on First Amendment issues as early as 2002. *See* Request for Comment on First Amendment Issues, 67 Fed. Reg. 34,942 (May 16, 2002); *see also*, *e.g.*, Comments of AdvaMed in response to Request for Comment on First Amendment Issues, Docket No. 02N-0209 (Sept. 13, 2002), https://web.archive.org/web/20030727105505/http://www.fda.gov/ohrms/dockets/dailys/02/Sep02/091602/80027d39.pdf; Comments of Pfizer in response to Request for Comment on First Amendment Issues, Docket No. 02N-0209 (Sept. 13, 2002), https://web.archive.org/web/20040225090954/http://www.fda.gov/ ohrms/dockets/dailys/02/Sep02/091602/80027f2d.pdf; Comments of PhRMA in response to Request for Comment on First Amendment Issues, Docket No. 02N-0209 (Sept. 13, 2002), https://web.archive.org/web/20090711155050/http://www.fda.gov/ohrms/dockets/dailys/02/Sep02/ 091602/80027d32.pdf.

II. BACKGROUND—THE FDA REGULATORY FRAMEWORK APPLICABLE TO OFF-LABEL COMMUNICATIONS

FDA's August 2, 2021, rule[5] implicates agency policies that have been put into place because of the role that off-label use plays in medical and surgical practice. Although the FDCA does not itself prohibit or even define "off-label use," that phrase is often used to refer to any departure from the directions for use that are provided in the official, FDA-approved labeling for a particular drug or medical device.[6] Deviations from such directions are extremely common in clinical practice, and in some scenarios off-label use represents the standard of care. Accordingly, FDA has established various policies to facilitate manufacturer communications about off-label uses. As discussed below, these "safe harbors" describe circumstances in which FDA will not enforce against a communication and/or provide recommendations for the manner in which manufacturers should handle such communications.

A. FDA Regulation of Off-Label Promotion

When FDA grants marketing authorization for a new drug or medical device, it also approves a highly technical document, which provides the information that, the agency has determined, is necessary for the product to be used safely and effectively. For a new drug, that document is known as the FDA-approved labeling and must conform to detailed content and format requirements set forth in FDA's regulations.[7] Under these requirements, the labeling must inform prescribers as to the circumstances, or conditions of use, in which the product will have a favorable risk-benefit ratio in clinical practice.[8] The required information specifies the disease or health condition and the patient population for which the drug is intended, explains the data on the basis of which the product was approved, and identifies the risks and limitations of use—including material uncertainties—that FDA has found clinically relevant.[9] The approved labeling for a drug or medical device does not contain all that is known about the product—in other words, the labeling cannot be "both authoritative and avant-garde."[10]

In general, the FDA regulatory framework aims to encourage the use of medical products in accordance with their approved labeling by prohibiting the promotion of

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5 Regulations Regarding "Intended Uses," 86 Fed. Reg. 41,383 (Aug. 2, 2021) (codified at 21 C.F.R. §§ 201.128, 801.4).

6 The scope of the FDCA provisions applicable to off-label use can be a matter of dispute in government investigations and enforcement actions, but has not been resolved (or even addressed) by the courts. The relevant statutory provision requires "adequate directions for use" in drug and medical device labeling, 21 U.S.C. § 352(f)(1), with "use" defined to mean the "purpose" for which the product is to be used. 21 C.F.R. § 201.5. A strict interpretation would require adequate directions for each disease or health condition for which the product is intended, leaving room for accurate promotional communications about unlabeled dosing regimens, for example. Under the broader interpretation, *any* departure from the approved product labeling—use of a drug not only for a new indication but also at a different dosage form or in a different line of therapy, for example—would give rise to FDCA liability.

7 21 C.F.R. §§ 201.56, 201.57.

8 21 C.F.R. § 201.57(c).

9 21 C.F.R. §§ 201.57(c)(2), (c)(9), (c)(9)(i)(B).

10 Robert Temple, *Legal Implications of the Package Insert*, 58 MED. CLINICS N. AM. 1151, 1155 (1974).

drugs and medical devices for off-label uses. Yet the FDCA expressly protects off-label use,[11] and does not prohibit "off-label promotion" in so many words. Rather, FDA relies on either or both of two misbranding theories, and on a "new drug" theory, in off-label promotion cases. FDA's authority to proceed against unapproved and misbranded products, together with its authority over manufacturer communications comprising "labeling," "advertisements," and certain oral statements, provides the foundation of federal regulation in this area.[12]

Under the first misbranding theory, FDA has asserted that off-label promotion violates the FDCA because it constitutes false or misleading labeling. Section 502(a) of the FDCA provides that "A drug . . . shall be deemed to be misbranded . . . [i]f its labeling is false or misleading in any particular."[13] Section 502(a) has been invoked with respect to drugs bearing literally false statements as well as drugs marketed with unsubstantiated therapeutic claims.[14] FDA does not typically invoke section 502(a) in cases involving allegedly false or misleading therapeutic claims. This is because the FDCA contains a separate mechanism authorizing FDA to require premarket approval of therapeutic claims. This mechanism arises under section 505(a) of the FDCA.[15]

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[11] 21 U.S.C. § 396 ("Nothing in this chapter shall be construed to limit or interfere with the authority of a health care practitioner to prescribe or administer any legally marketed device to a patient for any condition of disease within a legitimate health care practitioner-patient relationship."). See also 21 C.F.R. § 312.2(d) ("This part does not apply to the use in the practice of medicine for an unlabeled indication of a new drug . . . ."); Legal Status of Approved Labeling for Prescription Drugs; Prescribing for Uses Unapproved by the Food and Drug Administration, 37 Fed. Reg. 16,503 (Aug. 15, 1972) ("[I]t is clear that Congress did not intend the Food and Drug Administration to interfere with medical practice[.]").

[12] *See infra* note 14. *See also* Regulations Regarding "Intended Uses," 86 Fed. Reg. 41,383, 41,401 (Aug. 2, 2021) (codified at 21 C.F.R. §§ 201.128, 801.4).

[13] 21 U.S.C. § 352(a).

[14] *See, e.g.*, United States v. 4 Cases Slim–Mint Chewing Gum, 300 F.2d 144 (7th Cir. 1962) (affirming trial court denial of new trial in section 502(a) case in which jury found no false or misleading statements in labeling of diet gum); United States v. Articles of Drug Labeled Colchicine, 442 F. Supp. 1236, 1241 (S.D.N.Y. 1978) (holding that drugs violate section 502(a) when they are labeled "100 capsules" but contain only six capsules in each packet). For this provision to apply, a false or misleading statement must appear in a communication that qualifies as "labeling." 21 U.S.C. § 352(a) (referring to "*labeling*" that is "false or misleading in any particular") (emphasis added). "Labeling" is defined to mean "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." *Id.* § 321(m). The statutory term "label" means "a display of written, printed, or graphic matter upon the immediate container of any article." *Id.* § 321(k). Under *Kordel v. United States*, 335 U.S. 345 (1948), to "accompany" an article, matter must supplement or explain the product in connection with its distribution and sale. FDA regulations define "labeling" broadly to include "[b]rochures, 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." 21 C.F.R. § 202.1(l)(2). But "labeling does not include every writing which bears some relation to the product." United States v. 24 Bottles "STERLING VINEGAR AND HONEY AGED IN WOOD CIDER BLENDED WITH FINEST HONEY CONTENTS 1 PINT PRODUCT OF STERLING CIDER CO., INC., STERLING, MASS.," 338 F.2d 157, 158 (2d Cir. 1964). Press releases, for example, are not included within the list of communications identified as "labeling" in 21 C.F.R. § 202.1(l)(2). *See* 21 C.F.R. § 312.7(a) (ban on pre-approval promotion does not extend to "scientific findings," which is interpreted to include press releases). There are First Amendment arguments that FDA's authority over labeling should be interpreted to include only types of materials that are properly regarded as "commercial speech." *E.g.*, United States v. United States Dist. Ct. for the Cent. Dist. of Cal., 858 F.2d 534, 542 (9th Cir. 1988) ("scientific expression and debate" are at the "heartland" of protected speech); *accord* Miller v. California, 413 U.S. 15, 34 (1973).

[15] FDA prefers to use its "adequate directions" and "new drug" authorities because, under Section 502(a), FDA would have to go to court after a claim has already been made—and would have to demonstrate that labeling is false or misleading—in order to prevail. *See, e.g.*, United States v. Hoxsey Cancer Clinic,

Under the second misbranding theory, FDA contends that off-label promotion misbrands a drug because it "is evidence of" a new "intended use" for which adequate directions must be provided in labeling. Section 502(f)(1) of the FDCA provides that a drug "shall be deemed to be misbranded" unless its labeling contains "adequate directions for use."[16] "Use" in this context means "intended use," according to FDA, which is defined by regulation to mean "objective intent."[17] FDA's interpretation of section 502(f)(1) contends that a new intended use may be found based on a wide range of evidence, not limited to labeling, advertising, or oral statements by sales representatives or others acting on the seller's behalf. This interpretation is at the heart of the intended use rulemaking, discussed in further detail below.

Third, under the "unapproved new drug" theory, FDA has asserted that off-label promotion causes a drug to become an unapproved new drug. According to section 505(a) of the FDCA:

> No person shall introduce or deliver for introduction into interstate commerce any new drug, unless an approval of an application filed pursuant to subsection (b) [new drug application (NDA)] or (j) [abbreviated new drug application (ANDA)] is effective with respect to such drug.[18]

According to FDA, "an approved new drug that is marketed for a 'new use' becomes an unapproved new drug with respect to that use."[19]

All three theories depend on the content of "labeling." In general, FDA has recognized two categories of labeling under the FDCA: 1) official labeling, which is drafted by the manufacturer and revised through the premarket review process (e.g., the prescribing information or package insert); and 2) "promotional" labeling, which is tautologically defined to mean various manufacturer publications (e.g., brochures) "devised" for promotion of the product.[20] The FDCA and FDA regulations describe the kinds of statements in the latter type of labeling that would cause an approved new drug to become an unapproved new drug under section 505(a).[21] Under section 201(p)(1):

> The term "new drug" means—(1) Any drug . . . the composition of which is such that such drug is not generally recognized, among experts qualified by scientific training and experience to evaluate the safety and

198 F.2d 273, 278 (5th Cir. 1952) (Section 502(a) case involving ineffective cancer treatment marketed for more than thirty years).

16 21 U.S.C. § 352(f)(1).

17 21 C.F.R. § 201.128.

18 21 U.S.C. § 355(a).

19 Decision in Washington Legal Foundation v. Henney, 65 Fed. Reg. 14,286, 14,286 (Mar. 16, 2000). As with Section 502(a), this theory would apply only where the off-label statement occurs in a communication that qualifies as "labeling" under the FDCA.

20 *See* 21 U.S.C. § 352.

21 Section 505(a) and the "new drug" definition apply not only to pharmaceuticals but also to biological products, which FDA also regards as "drugs." A biological product marketed pursuant to an approved biologics license application (BLA) is not also required to have an approved NDA. *See* 42 U.S.C. § 262(j) (the FDCA applies to a biological product, "except that a product for which a license has been approved under subsection (a) shall not be required to have an approved application under section 505").

> effectiveness of drugs, as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof.[22]

In other words, whether a product is a "new drug" depends on the content of its labeling, and in particular the "conditions prescribed, recommended, or suggested" in that labeling. If "labeling" contains claims regarding the usefulness of a drug for a disease for which it was approved, then (under FDA's view) the drug is a "new drug" with respect to that use, and the use must be submitted to FDA for approval under section 505(a).[23]

As interpreted by FDA, the FDCA provisions discussed above limit the statements that may be made for prescription drugs by their respective manufacturers, but they do not ban all statements that are not set forth in approved labeling. The touchstone of the FDCA analysis is that promotional claims may not be for a "new use"; in other words, they do not have to appear in approved labeling, as long as they are "consistent with" the labeling. Thus, for example, FDA regulations expressly allow advertising claims that are not approved for use in a drug's labeling, including claims relating to effectiveness in particular patient subgroups and conditions, subject to any explicit limitations appearing in approved labeling (e.g., a limitation in the indication statement regarding the use of the drug in the particular subgroup or condition).[24] Accordingly, a manufacturer may lawfully promote its prescription drug product using claims that are not spelled out verbatim in the approved labeling, if those claims do not cause the product to be in violation of the relevant statutory provisions.

B. The Role of Off-Label Use in Patient Care

Although FDA asserts that off-label *promotion* is prohibited, off-label *use* is lawful.[25] Once a drug or device has been approved for marketing, a health care practitioner may, in treating patients, prescribe the product for uses not included in the approved labeling.[26] So long as the practitioner complies with state medical practice

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[22] 21 U.S.C. § 321(p)(1); *see also* 21 C.F.R. § 310.3(h) (describing the circumstances in which "newness . . . may arise").

[23] In a 2000 warning letter, for example, FDA—acting through its Division of Drug Marketing, Advertising, and Communications (DDMAC)—cited Section 505(a) in objecting to third-party press releases distributed by Celgene representatives recommending use of Thalomid (thalidomide) in cancer—an indication for which the drug had not yet been approved. In the first paragraph of the warning letter, DDMAC cited both Section 502(f) and Section 505(a). See Warning Letter from Thomas W. Abrams, R.Ph., M.B.A., Dir., DDMAC to John W. Jackson, CEO, Celgene Corp. (Apr. 21, 2000).

[24] 21 C.F.R. § 202.1(e)(6)(i); *see also* U.S. FOOD & DRUG ADMIN., MEDICAL PRODUCT COMMUNICATIONS THAT ARE CONSISTENT WITH THE FDA-REQUIRED LABELING—QUESTIONS AND ANSWERS: GUIDANCE FOR INDUSTRY 12 (June 2018), https://www.fda.gov/media/133619/download [hereinafter FDA, MEDICAL PRODUCT COMMUNICATIONS].

[25] Congress has prohibited the off-label prescribing of human growth hormone. *See* 21 U.S.C. § 333(e) (prohibiting the knowing distribution, or possession with intent to distribute, of human growth hormone—defined as somatrem, somatropin, or an analogue of either of them—for any use in humans other than the treatment of a disease or other recognized medical conditions, where such use has been "authorized" by FDA under 21 U.S.C. § 355 "and pursuant to the order of a physician").

[26] *See, e.g.*, 21 U.S.C. § 396; Proposed New Drug, Antibiotic, and Biologic Drug Product Regulations, 48 Fed. Reg. 26,720, 26,733 (proposed June 9, 1983); 21 C.F.R. § 312.2(d) (exemption from FDA regulations for "the use in the practice of medicine for an unlabeled indication of a new drug product approved" by the agency); Legal Status of Approved Labeling for Prescription Drugs; Prescribing for Uses Unapproved by the Food and Drug Administration, 37 Fed. Reg. 16,503, 16,503 (Aug. 15, 1972) ("[T]he physician may, as part of the practice of medicine, lawfully prescribe a different dosage for his patient, or

standards he or she may depart from the conditions of use set forth in approved labeling.[27]

Off-label uses not only are lawful but also are "common, can be a source of innovation, and in some settings may represent the standard of care."[28] Doctors must often rely on off-label use "[b]ecause the pace of medical discovery runs ahead of the FDA's regulatory machinery," rendering off-label uses the "'state-of-the-art' treatment."[29] "For some diseases, . . . off-label uses either are the only therapies available, or are the therapies of choice."[30] Indeed, "a drug given off-label may have been proven to be safer and more beneficial than any drug labeled for that disease."[31]

One 2003 study found that 9% of surveyed physicians prescribe off-label more than 40% of the time, and only 18% of physicians prescribe off-label less than 5% of the time.[32] The rest of the surveyed physicians fell somewhere in the middle or were not sure of their prescribing habits, suggesting a lack of knowledge among some respondents regarding the on- or off-label status of the products they prescribe.[33] A 2005 American Medical Association (AMA) resolution noted: "[u]p to date, clinically appropriate medical practice at times requires the use of pharmaceuticals for 'off-label' indications."[34] In 1993, FDA observed, "[i]n practice, surgeons often use orthopedic screws which FDA has cleared for other purposes . . . as pedicle screws" because "surgery utilizing pedicle screws represent[ed] the best available treatment

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may otherwise vary the conditions of use from those approved in the package insert, without informing or obtaining the approval of the Food and Drug Administration.").

[27] *See* Ass'n of Am. Physicians & Surgeons, Inc. v. FDA, 226 F. Supp. 2d 204, 206 (D.D.C. 2002) ("when the FDA approves a drug, it approves the drug only for the particular use for which it was tested, but after the drug is approved for a particular use, 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) (recognizing "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").

[28] Donna T. Chen, Matthew K. Wynia, Rachael M. Moloney & G. Caleb Alexander, *U.S. Physician Knowledge of the FDA-Approved Indications and Evidence Base for Commonly Prescribed Drugs: Results of a National Survey*, 18 PHARMACOEPIDEMIOLOGY & DRUG SAFETY 1094, 1094 (2009) (footnotes omitted).

[29] Richardson v. Miller, 44 S.W.3d 1, 13 n.11 (Tenn. Ct. App. 2000); *see also* J. HOWARD BEALES III, NEW USES FOR OLD DRUGS 303 (Robert B. Helms ed. 1996) (reporting that off-label uses that later come to be recognized by FDA appear in official compendia on average 2.5 years before FDA recognition) (internal citation omitted).

[30] Comments of the Medical Information Working Group on FDA's "Good Reprint Practices" Draft Guidance, 4 (Apr. 18, 2008) (citing Susan G. Poole & Michael J. Dooley, *Off-Label Prescribing in Oncology*, 12 SUPPORTIVE CARE CANCER 302 (2004)).

[31] *Off-Label Drug Use and FDA Review of Supplemental Drug Applications, Hearing Before the Subcomm. On Human Resources and Intergovernmental Relations of the H. Comm. On Government Reform and Oversight*, 104th Cong. 12 (1996) (statement of Sarah F. Jaggar, Director of Health Services Quality and Public Health Issues, General Accounting Office).

[32] Daniel B. Klein & Alexander T. Tabarrok, *Do Off-Label Drug Practices Argue Against FDA Efficacy Requirements? Testing an Argument by Structured Conversations with Experts*, INDEP. INS. WORKING PAPER NO. 47, 12 (Apr. 16, 2003).

[33] *Id.*

[34] Memorandum of the AMA House of Delegates, Resolution 820, Off-Label Use of Pharmaceuticals (Sept. 21, 2005) (emphasis added) [hereinafter Memorandum].

for patients."[35] Where off-label use constitutes the standard of care, non-use can raise the specter of malpractice claims for doctors—making off-label use of drugs not just permissible, but indeed effectively mandatory.[36]

One medical field particularly dependent on off-label use is oncology. As early as 1991, the U.S. Government Accountability Office (GAO) issued a report documenting that "[a] third of all drug administrations to cancer patients were off-label, and more than half of the patients received at least one off-label drug."[37] In 2005, the National Comprehensive Cancer Network estimated that "50% to 75% of all uses of drugs and biologics in cancer care in the United States are off-label."[38] Off-label use is so widespread in oncology practice that federal law requires the Centers for Medicare and Medicaid Services (CMS) to reimburse for off-label uses of anticancer drugs if the use appears in an official medical compendia.[39] The American Cancer Society explains that:

> [o]ff-label drug use is common in cancer treatment because:
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> - Some cancer drugs are found to work against many different kinds of tumors.
> - Chemotherapy treatments often combine drugs. These combinations might include one or more drugs not approved for that disease. Also, drug combinations change over time as doctors study different ones to find out which work best.
> - Cancer treatment is always changing and improving.
> - Oncologists (cancer doctors) and their patients are often faced with problems that have few approved treatment options. This is especially true for less common types of cancer.
> - Oncologists and their patient may be more willing to try off-label drugs than other medical specialties.[40]

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[35] U.S. FOOD & DRUG ADMIN., UPDATE ON PEDICLE SCREWS (1993); AMERICAN ACADEMY OF ORTHOPEDIC SURGEONS, POSITION PAPER (Oct. 27, 1993).

[36] *See* Buckman Co. v. Plaintiffs' Legal Comm., 531 U.S. 341, 350–51, n.5 (2001); Washington Legal Found. v. Friedman, 202 F.3d 331, 333 (D.C. Cir. 2000); *see also* 1997 Annual Meeting of the American Medical Association, 4, Reports of the Council on Scientific Affairs, http://tinyurl.com/ykowbgx ("the prescribing of drugs for unlabeled uses is often necessary for optimal patient care") (on file with author, link no longer available).

[37] U.S. GOV'T ACCOUNTABILITY OFF., PEMD-91-14, OFF-LABEL DRUGS: REIMBURSEMENT POLICIES CONSTRAIN PHYSICIANS IN THEIR CHOICE OF CANCER THERAPIES 3 (1991), https://www.gao.gov/assets/pemd-91-14.pdf.

[38] Michael Soares, *"Off-Label" Indications for Oncology Drug Use and Drug Compendia: History and Current Status*, 1 J. ONCOLOGY PRAC. 102, 104 (2005).

[39] *See* 42 U.S.C. §§ 1395x(t)(2), 1396r-8(g)(1)(B)(i), 1396r-8(k)(6).

[40] AM. CANCER SOC'Y, OFF-LABEL DRUG USE (last revised Mar. 17, 2015), https://www.cancer.org/content/dam/CRC/PDF/Public/7220.pdf (last visited Aug. 21, 2023); *see also Off-Label Drug Use in Cancer Treatment*, NAT'L CANCER INST. (last reviewed Jan. 13, 2022), https://www.cancer.gov/about-cancer/treatment/drugs/off-label (last visited Aug. 21, 2023); *see also* John E. Osborn, *Can I Tell You The Truth—A Comparative Perspective on Regulating Off-Label Scientific and Medical Information*, 10 YALE J. HEALTH POL'Y, L. & ETHICS 299, 336–38 (2010) (describing the off-label use of Avastin and Lucentis to treat AMD [age-related macular degeneration]).

A similar situation exists in psychiatry. Like oncology, psychiatry is a field in which multiple treatment attempts and methods may be necessary before appropriate treatment can be found for a particular patient. It also is a field, like oncology, in which a drug that treats one disease or disorder may prove useful in treating a related or similar one. Patients often are treated based on symptoms rather than on a specific diagnosis, and there are even psychiatric disorders for which no approved drug has an indication, such that off-label use is the only option for drug therapy.[41] Even if FDA has approved a drug for a particular condition, the patient may fall outside the labeled patient population, or might need a higher or lower dosage.[42] As a result, uses of approved drugs in ways that depart from approved labeling are common in psychiatry.[43]

Off-label use of medical devices constitutes the standard of care across a variety of medical fields. According to one report, "[s]ome 70% of kidney dialysis patients use their dialysis equipment in an off-label manner."[44] A study from 1993 found that the most commonly mentioned off-label uses reported by manufacturers to FDA involved medical devices for osteoporosis treatments.[45] Doctors agree that off-label use of devices "has become an important method by which medical knowledge is expanded."[46] In addition, "[i]n orthopaedics, off-label use has [become] a common and beneficial component in the evolution of total joint replacement technology." Indeed, "30% of total hip arthroplasty (THA) and 37% of total knee arthroplasty (TKA) procedures, using regular off-the-shelf implants, are performed in groups of patients outside those approved by [FDA]."[47] Similarly, "[o]ff-label use of medical devices is a common practice among vascular specialists."[48]

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[41] *See* Katrina Furvey & Kristen Wilkens, *Prescribing "Off-Label": What Should a Physician Disclose?*, 18 AMA J. ETHICS 587, 588–89 (2016); *see also* Kavi K. Devulapalli & Henry A. Nasrallah, *An Analysis of the High Psychotropic Off-Label Use in Psychiatric Disorders*, 2 ASIAN J. PSYCH. 29 (2009).

[42] Andrew McKean & Erik Monasterio, *Off-Label Use of Atypical Antipsychotics*, 26 CNS DRUGS 383 (2012) ("In psychiatry, off-label prescribing is common and gives clinicians scope to treat patients who are refractory to standard therapy or where there is no licensed medication for an indication.").

[43] *See* Randall S. Stafford, *Regulating Off-Label Drug Use–Rethinking the Role of the FDA*, 358 NEW ENGL. J. MED. 1427, 1427 (2008); G. Caleb Alexander, Sarah A. Gallagher, Anthony Mascola, Rachael M. Moloney & Randall S. Stafford., *Increasing Off-Label Use of Antipsychotic Medications in the United States, 1995-2008*, 20 PHARMACOEPIDEMIOLOGY & DRUG SAFETY 177, 181 (2011).

[44] James M. Beck & Elizabeth D. Azari, *FDA, Off-Label Use, and Informed Consent: Debunking Myths and Misconceptions*, 53 FOOD & DRUG L.J. 71, 80 n.77 (1998) (citing *FDA and Dialyzer Makers Spar Over Device Reuse*, FOOD & DRUG LETTER (Apr. 8, 1994)).

[45] *Id.* at 80 n.78 (citing *Off-label Use of Provera, Didronel For Osteoporosis*, THE PINK SHEET, 1 (Dec. 20, 1993)).

[46] Michael R. Zindrick, *Orthopaedic Surgery and Food and Drug Administration Off-Label Uses*, 6 CLINICAL ORTHOPAEDICS & RELATED RSCH. 31, 31 (Sept. 2000); *see also* Barbara Buch, *FDA Medical Device Approval: Things You Didn't Learn in Medical School or Residency*, 29 AM. J. ORTHOPEDICS 407, 411 (Aug. 2007) (stating that off-label use of devices "is often appropriate and may represent the standard of practice").

[47] Keith Tucker, Klaus-Peter Günther, Per Kjaersgaard-Andersen, Jörg Lützner, Jan Philippe Kretzer, Rob G. H. H. Nelissen, Toni Lange & Luigi Zagraet, *EFORT Recommendations for Off-Label Use, Mix & Match and Mismatch in Hip and Knee Arthroplasty*, EFORT OPEN REVS. 982, 987 (2021).

[48] O. William Brown, *Legal Implications of Pushing the Endovascular Envelope*, 56 VASC. LEGAL FORUM 273 (2021).

C. FDA "Safe Harbor" Policies Permitting Off-Label Information Dissemination

FDA has repeatedly recognized the legitimacy and public health necessity of off-label use. For example, in 1972, FDA stated that "Congress did not intend the Food and Drug Administration to interfere with medical practice" by seeking to regulate off-label use.[49] In 1998, FDA provided guidance to institutional review boards regarding off-label use, stating that "[g]ood medical practice and the best interests of the patient require that physicians use legally available drugs, biologics and devices according to their best knowledge and judgment."[50] And 2009 guidance from FDA explained that "off-label uses or treatment regimens may be important and may even constitute a medically recognized standard of care."[51] In promulgating a variety of policies providing recommendations for manufacturers interested in disseminating off-label information, FDA has attempted to strike a "delicate balance" between FDCA enforcement and the requirements of patient care.[52]

A key attribute of the safe harbors for manufacturer off-label communications involves the distinction, not set forth in the FDCA but a recurring theme in FDA's own pronouncements, between the promotion of a drug or medical device for an off-label use on the one hand, and the non-promotional dissemination of information about such a use on the other. As noted below, in the 1990s there emerged the idea that the FDCA's labeling and advertising provisions applied to "promotion," while the non-promotional "dissemination" of off-label information would not be regulated by FDA under the statute. The promotion-dissemination distinction carried through in other FDA statements, notably in litigation statements in the *Allergan* case, discussed below. There, a senior FDA official indicated that the statute extended only to statements that "prescribed, recommended, or suggested" an off-label use, meaning—for example—that a manufacturer was free to provide information about the risks of an off-label use without fear of enforcement action, even to the extent of incorporating such information into the official approved labeling for the product.[53] This supposed promotion/non-promotion distinction has been a feature of FDA's approach to off-

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[49] Legal Status of Approved Labeling for Prescription Drugs; Prescribing for Uses Unapproved by the Food and Drug Administration, 37 Fed. Reg. 16,503, 16,504 (Aug. 15, 1972).

[50] U.S. FOOD & DRUG ADMIN., "OFF-LABEL" AND INVESTIGATIONAL USE OF MARKETED DRUGS, BIOLOGICS, AND MEDICAL DEVICES, GUIDANCE FOR INSTITUTIONAL REVIEW BOARDS AND CLINICAL INVESTIGATORS (1998); *see also* Dissemination of Information on Unapproved/New Uses for Marketed Drugs, Biologics, and Devices, 63 Fed. Reg. 31,143, 31,153 (June 8, 1998) ("FDA has long recognized that in certain circumstances, new (off-label) uses of approved products are appropriate, rational, and accepted medical practice.").

[51] U.S. FOOD & DRUG ADMIN., 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 OR CLEARED MEDICAL DEVICES 2 (2009)

[52] *See, e.g.*, Advertising and Promotion; Guidances, 61 Fed. Reg. 52,800, 52,800 (Oct. 8, 1996) (noting that agency policies should "strike the proper balance between the need for an exchange of reliable scientific data and information within the health care community, and the statutory requirements that prohibit companies from promoting products for unapproved uses"); *see also* Memorandum, *supra* note 34, at 20 ("FDA . . . has sought to strike a careful balance, supporting medical decision-making for patients in the absence of better options, but doing so without undermining the measures designed to incentivize the development and approval/clearance of medical products that would reduce the need to rely on unapproved use, in light of its risks.").

[53] See discussion *infra* Section II.C.5.

label communications, though it has not provided a complete answer to the constitutional questions confronting the agency. Nor have the safe harbors scrupulously adhered to this distinction, as will become evident from the discussion below.

As of August 2021, when the final rule amending the intended use regulations was published, FDA had set forth its approach to manufacturer dissemination of off-label information in a wide variety of pronouncements. These included safe harbor guidance documents cited in the preamble accompanying the August 2021 final rule. They also included a regulation, codified at 21 C.F.R. § 312.7(a), which recognized a category of permissible communication known as "scientific exchange." The scientific exchange regulation and guidance documents are discussed chronologically below, along with key developments that influenced FDA to adjust its approach over time.

1. Early Antecedents: Scientific Exchange and Drug Labeling Rulemaking (1962–1972)

The initial period in FDA's long history of developing and refining its approach to manufacturer off-label communications is characterized by two rulemaking proceedings. The first established in FDA's regulations a "scientific exchange" limitation on the agency's ability to prohibit manufacturers from promoting investigational new drugs.[54] The second, in a proposed rule that was never finalized, responded to specific concerns about off-label use and led FDA to articulate the so-called "practice of medicine policy"—setting forth the basic idea that the agency will not seek to interfere in the decision to prescribe or use a medical product off-label as part of legitimate medical or surgical practice. This idea was later incorporated into FDA regulations and into the FDCA.[55]

On August 10, 1962, FDA published a notice of proposed rulemaking to amend the new drug regulations (then codified at 21 C.F.R. § 130.3).[56] Proposed § 130.3(a)(10) provided that a manufacturer that has initiated clinical investigations to study a new drug candidate may not, directly or through others, misrepresent the investigational status of the drug by claiming it is either "safe" or "useful for the purposes for which it is offered for investigation."[57] The final version of the rule, published in 1963, retained that prohibition (with modest changes) and added the "scientific exchange" principle that remains in effect today. It states:

> This regulation is not intended to restrict the full exchange of scientific information concerning the drug, including dissemination of scientific findings in scientific or lay communications media; its sole intent is to

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[54] Procedural and Interpretive Regulations; Investigational Rule, 28 Fed. Reg. 179, 180 (Jan. 8, 1963).

[55] Food And Drug Modernization Act of 1997, Pub. L. No. 105-115, § 401(b)(1)(B), 111 Stat. 2296, 2356 (codified at 21 U.S.C. § 360aaa).

[56] New Drugs for Investigational Use, 27 Fed. Reg. 7,990, 7,900 (proposed Aug. 10, 1962). I am aware of no evidence that any version of § 312.7(a) existed before 1962. In particular, the promulgation history of § 130.3 contains nothing of relevance. *See* 22 Fed. Reg. 3,041 (Apr. 30, 1957); 22 Fed. Reg. 385 (Jan. 18, 1957); 21 Fed. Reg. 5,576 (July 25, 1956); 21 Fed. Reg. 3,690 (May 30, 1956); 20 Fed. Reg. 6,584 (Sept. 8, 1955); 13 Fed. Reg. 6,555 (Nov. 8, 1948); 13 Fed. Reg. 3,972 (July 14, 1948); 3 Fed. Reg. 1,846 (July 23, 1938).

[57] 27 Fed. Reg. at 7,991 ("Neither the sponsor nor any person acting for or on behalf of the sponsor shall disseminate any labeling, advertising, public relations statements, or news releases, representing the drug to be safe or useful for the purposes for which it is offered for investigation.").

> restrict promotional claims of safety or effectiveness by the sponsor while the drug is under investigation to establish its safety or effectiveness.[58]

At the time, FDA did not include preambles in its rulemaking documents, so the reason for the change is not evident from the official record. According to a journal article published the following year and authored by the Director of the Division of New Drugs in the Bureau of Medicine at FDA (the predecessor of the Center for Drug Evaluation and Research (CDER)), however:

> This provision was prompted by instances of extensive promotion of new drugs distributed under the investigational legend. In consideration of this point in the proposed regulations, fear was expressed that this would prevent the presentation or publication of scientific papers or reporting of such in the lay press. It has been clearly stated that it is not the intent to do so or to prevent full exchange of scientific information. This has become evident during the short period since the regulations have become effective.[59]

At this point, the regulation seemed to mean only that a manufacturer could not engage in frank promotion of a drug before FDA approval.[60]

In 1972, FDA proposed a rule that would have regulated off-label uses of prescription drugs.[61] Under the proposal, FDA would have been "obligated" to take one or more enumerated actions to address an "unapproved use" that either endangers or benefits patients or the public health. The agency would have been required, for example, to revise the package insert to add a specific contraindication or warning against the unapproved use.[62]

In the preamble accompanying the proposed rule, FDA set forth what has become the seminal statement of the agency's policy of non-interference in medical practice:

> Once the new drug is in a local pharmacy after interstate shipment, the physician may, as part of the practice of medicine, lawfully prescribe a different dosage for his patient, or may otherwise vary the conditions of use from those approved in the package insert, without informing or obtaining the approval of the Food and Drug Administration.
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> This interpretation of the Act is consistent with congressional intent as indicated in the legislative history of the 1938 Act and the drug amendments of 1962. Throughout the debate leading to enactment, there

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[58] *See* 28 Fed. Reg. at 180. The revised prohibition provides: "Neither the sponsor nor any person acting for or on behalf of the sponsor shall disseminate any promotional material representing that the drug being distributed interstate for investigational use is safe or useful for the purposes for which it is under investigation." *Id.*

[59] Ralph G. Smith, *Government Control of New Drug Testing and Introduction*, 19 FOOD, DRUG, COSM. L.J. 305, 308 (1964).

[60] Nearly twenty years later, an FDA official affirmed that this language authorized FDA to object to safety and efficacy claims made prior to approval. Peter H. Rheinstein, *A Head Start, A Broader Audience, and an Emphasis on Difference: The New Frontiers of Prescription Drug Promotion*, 37 FOOD, DRUG, COSM. L.J. 330, 332 (1982) (author was then Acting Deputy Director, Office of Drugs, National Center for Drugs and Biologics, FDA, and previously, Director, Division of Drug Advertising and Labeling).

[61] Legal Status of Approved Labeling for Prescription Drugs; Prescribing for Uses Unapproved by the Food and Drug Administration, 37 Fed. Reg. 16,503, 16,503 (Aug. 15, 1972).

[62] *Id.* at 16,504.

> were repeated statements that Congress did not intend the Food and Drug Administration to interfere with medical practice and references to the understanding that the bill did not purport to regulate the practice of medicine as between the physician and the patient. . . .
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> [A]lthough it is clear that Congress did not intend the Food and Drug Administration to regulate or interfere with the practice of medicine, it is equally clear that it did intend that the Food and Drug Administration determine those drugs for which there exists substantial evidence of safety and effectiveness and thus will be available for prescribing by the medical profession, and additionally, what information about the drugs constitutes truthful, accurate, and full disclosure to permit safe and effective prescription by the physician. As the law now stands, therefore, the Food and Drug Administration is charged with the responsibility for judging the safety and effectiveness of drugs and the truthfulness of their labeling. The physician is then responsible for making the final judgment as to which, if any, of the available drugs his patient will receive in the light of the information contained in their labeling and other adequate scientific data available to him.[63]

FDA thus recognized that the agency's statutory authority to control the market introduction and labeling of new drugs did not encompass the power to restrict the uses to which approved drugs might be put.[64] FDA also expressly recognized that physicians rely not only on labeling, described elsewhere in the preamble as "a full, complete, honest, and accurate appraisal of the important facts that have reliably been proved about the drug," but also on "other adequate scientific data."[65]

The preamble contemplated that these "scientific data" would not come from the manufacturer. FDA stated:

> [W]here a manufacturer or his representative, or any person in the chain of distribution, does anything that directly or indirectly suggests to the physician or to the patient that an approved drug may properly be used for

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[63] *Id.* at 16,503–04.

[64] To this extent, the 1972 preamble statement is consistent with at least one earlier statement. *See* Herbert L. Ley, *The Citizen, Chemicals, and Controls, Address at Harvard Medical School Alumni Day* (June 4, 1971) (the physician is free "to prescribe the drug as they see fit"), *reprinted in New Drugs for Nonapproved Purposes (Methotrexate for Psoriasis): Hearings Before a Subcomm. of the House Comm. on Gov't Operations*, 92 Cong. 131, 133 (1971). According to one prominent commentator, FDA "was concerned" about "improper prescribing," but "was under great pressure from the American Medical Association not to tell the doctor what he or she could prescribe." *See* David A. Kessler, *Regulating the Prescribing of Human Drugs for Nonapproved Uses under the Food, Drug, and Cosmetic Act*, 15 HARV. J. ON LEGIS. 693, 698 n.13 (1977). Kessler indicated that FDA "chose to deal with the problem [of off-label prescribing] as an educational matter." *Id.* The cited hearings corroborate this account. Kessler suggests that the 1972 preamble was precipitated by "chiding" at these hearings about FDA's lack of explicit policy on off-label prescribing. *Id.* at 698. On at least one previous occasion, FDA was roundly criticized for advising the author of a medical textbook that he should make revisions warning against a dosage he had recommended after children died from receiving the higher dosage. After the criticism, FDA assured physicians that it had no intention of regulating prescribing decisions. Herbert L. Ley, *FDA Papers (Letter to the Editor)*, 8 CLINICAL PHARMACOLOGY & THERAPEUTICS 749 (1967). FDA was thus buffeted both by congressional demands that it address off-label prescribing and by physician resistance to such regulation.

[65] 37 Fed. Reg. at 16,504.

> unapproved uses for which it is neither labeled nor advertised, that action constitutes a direct violation of the Act and is punishable accordingly.[66]

The agency thus stated that it viewed dissemination of off-label information by a manufacturer as a statutory violation.

The proposed rule was fiercely opposed, particularly by physicians. In a 1972 editorial headlined "Eternal Vigilance—The Price of Liberty,"[67] the American Medical Association voiced its criticism. FDA also received critical letters from physicians.[68] Faced with this opposition, FDA did not issue the rule in final form.[69]

2. The IND and NDA Rewrites and Reagan-Era Regulatory Reform

The impact of FDA's 1972 foray into regulating off-label prescribing and off-label information dissemination was blunted considerably by developments in the 1980s. A 1982 "drug bulletin" emphasized that FDA regarded off-label use as "accepted medical practice," for example.[70] Health care practitioners were thus reassured that FDA would not seek to interfere in off-label prescribing undertaken as a constituent part of medical practice.

As FDA was revising its investigational new drug regulations, known as the "IND Rewrite" process, the agency also sought to provide guidance to industry with respect to an issue closely related to scientific exchange—and thereby effectively established the second safe harbor permitting manufacturers to disseminate information relating to off-label uses.[71] On April 22, 1982, recognizing that no regulation defined or addressed "the concept of 'solicited and unsolicited requests,'" FDA's Division of Drug Advertising and Labeling (DDAL) issued a one-page document providing "clarification and guidance" to manufacturers on this issue.[72]

The document asserted that, under FDCA §§ 502(f) and 201(m) and 21 C.F.R. §§ 201.100(d)(1) and 202.1(l)(2), "all matter descriptive of, or containing drug information supplied by or on behalf of the manufacturer, packer or distributor of the drug, constitutes labeling."[73] Nevertheless, DDAL said, it would not apply the labeling provisions of the FDCA to a pharmaceutical manufacturer's responses to "any and all *unsolicited* requests received from outside the company for information about a drug manufactured, distributed or repacked by the company."[74] Instead, DDAL would view

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[66] *Id.*

[67] *See* Gregory J. Bierne, *Eternal Vigilance—The Price of Liberty*, 222 JAMA 1553 (1972).

[68] *See FDA's Growing Influence on Your Practice*, 15 MED. WORLD NEWS 35, 46 (Mar. 1, 1974); *see also* Letter from American Soc. of Hosp. Pharmacists to FDA Commissioner Donald Kennedy, at 5 (Aug. 9, 1977).

[69] In 1991, FDA considered and rejected withdrawing the 1972 proposed rule. *See* Withdrawal of Certain Pre-1986 Proposed Rules; Opportunity for Public Comment, 56 Fed. Reg. 42,668, 42,669 (Aug. 28, 1991).

[70] *Use of Approved Drugs for Unlabeled Indications*, 12 FDA DRUG BULL. 4, 5 (Apr. 1982).

[71] *See* New Drug, Antibiotic, and Biologic Drug Product Regulations, 52 Fed. Reg. 8,798 (Mar. 19, 1987).

[72] U.S. FOOD & DRUG ADMIN., *Position on the Concept of Solicited and Unsolicited Requests* (Apr. 22, 1982).

[73] *Id.*

[74] *Id.*

these communications as "personal communication between the requestor and firm."[75] DDAL observed that this approach was "consistent with" 21 C.F.R. § 312.7.[76]

In the policy, DDAL included several important limitations. First, a company could not, through its sales force or by providing business reply cards, precipitate or expressly encourage a request for off-label information.[77] A company's response to a solicited request would be treated as labeling.[78] Second, DDAL "strongly recommended" that the manufacturer include in each response "some positive statement consistent with the approved labeling about the drug's use or dosage" and a reference to the accompanying full package insert.[79] Third, DDAL made clear that it would suspend the policy, either in particular cases or in its entirety, "[i]f problems or abuses are noted."[80]

In 1983, FDA published another notice of proposed rulemaking to amend the investigational new drug regulations.[81] FDA proposed to revise § 130.3(a)(10) as follows:

> § 312.7 Promotion and sale of investigational drugs.
>
> (a) *Promotion of an investigational new drug.* 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 provision is not intended to restrict the full exchange of scientific information concerning the drug, including dissemination of scientific findings in scientific or lay media: Rather, its intent is to restrict promotional claims of safety or effectiveness of the drug for a use for which it is under investigation and to preclude commercialization of the drug before it is approved for commercial distribution.[82]

According to FDA, "[t]he proposal would retain, essentially unchanged, the current provisions prohibiting promotion and commercialization of investigational drugs."[83] The final version of § 312.7, published in March 1987, was identical to the 1983 proposal.[84] Since the rule was finalized, FDA has resisted revising the regulation and,

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[75] *Id.*

[76] *Id.* It is significant that DDAL did not say the policy was based on or essentially the same as that regulation. Part 312 applies to statements about off-label uses for which a drug is under investigation, and appears to focus principally on a manufacturer or clinical investigator's proactive dissemination of clinical trial data to the media. The unsolicited requests policy applies to all off-label uses and covers any off-label information that might be provided by a manufacturer to a member of the public.

[77] *Id.*

[78] *Id.*

[79] *Id.*

[80] *Id.*

[81] Proposed New Drug, Antibiotic, and Biologic Drug Product Regulations, 48 Fed. Reg. 26,720, 26,720 (proposed June 9, 1983).

[82] *Id.* at 26,737.

[83] *Id.* at 26,734.

[84] New Drug, Antibiotic, and Biologic Drug Product Regulations, 52 Fed. Reg. 8,798, 8,833 (Mar. 19, 1987).

most recently in the intended use rulemaking, rejected comments from industry asking the agency to clarify the scope of scientific exchange.[85]

3. The Kessler Era—The 1990s

During David Kessler's tenure as Commissioner of FDA, the agency sought to crack down on manufacturer dissemination of information about off-label uses.[86] In the early 1990s, FDA undertook a broad review of activities the agency said were promotional but disguised as education. Consistent with the new Commissioner's position that all statements made by or on behalf of drug manufacturers were within the agency's regulatory authority,[87] FDA began experimenting with new policies designed to regulate the content of company communications that, until then, had been seen as beyond the agency's reach.[88]

In May 1991, FDA announced that it had entered into an agreement with Bristol-Myers Squibb to settle allegations that the company had promoted several of its cancer drugs off-label by disseminating a scientific oncology publication, "Oncology Commentary," to physicians.[89] According to FDA's spokesperson, the agency's concern was not with off-label information dissemination per se; rather, it objected to the dissemination of promotional information under the guise of scientific information.[90] FDA was "especially concerned," said the spokesperson, "about drug companies that sponsor conferences, seminars and speaking tours solely to promote their own products. What we're saying is scientific and educational material is fine to be distributed and promotional material is fine but you can't distribute one as if it were the other."[91]

The following month, in June 1991, at a congressional hearing, Commissioner Kessler pledged to use the "full force of the law" to clamp down on pharmaceutical companies that promote their products for off-label uses.[92] Commissioner Kessler also

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[85] *See* Regulations Regarding "Intended Uses," 86 Fed. Reg. 41,383, 41,383 (Aug. 2, 2021) (codified at 21 C.F.R. §§ 201.128, 801.4).

[86] At least one agency official had expressed a broad view of FDA's authority over off-label information before Kessler's appointment. Speech by Kenneth R. Feather, Acting Director, FDA Division of Drug Advertising and Labeling, before the Annual Meeting of the Pharmaceutical Manufacturers of America Marketing Section, Mar. 14, 1989, *reprinted in* PETER B. HUTT & RICHARD A. MERRILL, FOOD AND DRUG LAW: CASES AND MATERIALS 462 (2d ed. 1991).

[87] In 1990, Kessler expressed the view that FDA had authority to regulate "virtually any material issued by or sponsored by a drug manufacturer." David A. Kessler & Wayne L. Pines, *The Federal Regulation of Prescription Drug Advertising and Promotion*, 264 JAMA 2,409, 2,409 (1990).

[88] Nancy Benac, *FDA Getting Tough On Disguised Drug Promotions*, AP (May 30, 1991) (available via Lexis/Nexis); Lars Noah & Barbara A. Noah, *Liberating Commercial Speech: Product Labeling Controls and the First Amendment*, 47 FLA. L. REV. 63, 72 (1995) (FDA regulation of CME "represents a significant extension of the FDA's traditional controls over the labeling and advertising of prescription drugs and medical devices, potentially limiting the robust exchange of scientific information about important therapeutic advances.") (citation omitted).

[89] *See Journal Reprints with "Reference To" Unapproved Uses Would be Allowed Under FDA Promotion Reform: Textbook Dissemination Okay if Off-Label Use not "Highlighted,"* THE PINK SHEET, 1 (Nov. 27, 1995) [hereinafter *Journal Reprints*]; Benac, *supra* note 88. FDA's treatment of the publication as promotional was consistent with Kessler's view that FDA had authority to regulate "virtually any material issued by or sponsored by a drug manufacturer." *See* Kessler & Pines, *supra* note 87, at 1,409.

[90] Benac, *supra* note 88.

[91] *Id.*

[92] Teri Randall, *FDA Scrutinizes 'Off-Label' Promotions*, 266 JAMA 11 (1991).

promised that physicians acting on behalf of those companies would also be subject to the law.[93]

In October 1991, FDA began developing a new written policy on off-label information dissemination in scientific and educational settings. Specifically, the agency published a draft "concept paper" describing its views on manufacturer-sponsored or -funded off-label communications as part of continuing medical education (CME) and similar events.[94] In this document, the Division of Drug Marketing, Advertising, and Communications (DDMAC)—the successor to DDAL—set forth a proposed regulatory approach applicable to "drug company supported activities in scientific or educational contexts."[95] The draft concept paper generated an enormous number of comments, most of them negative.[96] Some companies involved in producing continuing education activities objected to FDA's approach on the ground that regulated manufacturers would no longer fund them for fear of enforcement action.[97]

On March 23, 1992, FDA refused to allow a manufacturer to distribute free copies of a recognized, widely used oncology textbook at a major medical conference, because the textbook mentioned off-label uses of several of the manufacturer's drugs.[98] In response, in May 1992, the textbook's publisher wrote the agency in protest, noting that publishers had begun to feel the effects of FDA's crackdown on educational materials.[99] According to the publisher, a different manufacturer the previous year had declined to fund or distribute a journal supplement on benign prostatic hyperplasia because of concern over FDA enforcement.[100] In another case discussed in the publisher's letter, yet a third manufacturer had bought 4,000 copies of a textbook on magnetic resonance imaging but did not distribute them.[101]

In November 1992, FDA described its "longstanding policy" on manufacturer communication of scientific information to health care practitioners in a slightly revised version of the October 1991 concept paper, this one designated a "draft policy

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[93] *Id.*

[94] U.S. FOOD & DRUG ADMIN., *Drug Company Supported Activities In Scientific or Educational Contexts* (Oct. 26, 1991). Earlier that year, the *New England Journal of Medicine* published an opinion piece by Dr. Kessler which indicated that his understanding of the scope of "scientific and educational activities" included "programs of continuing medical education, grand rounds, press releases and press conferences, videotaped news releases, journals, and special supplements to otherwise peer-reviewed journals." David A. Kessler, *Drug Promotion and Scientific Exchange—The Role of the Clinical Investigator*, 325 NEW ENG. J. MED. 201 (1991).

[95] *Drug Company Supported Activities In Scientific or Educational Contexts*, *supra* note 94.

[96] *See, e.g.*, Steve Taylor, *1,000 Letters to FDA Provoked CME Concept Paper Rewrite*, DICKINSON'S FDA, at 8–9 (Feb. 15, 1992) (estimating that 75% of the comments on the Draft Concept Paper were negative).

[97] *See* Dennis K. Wentz, Arthur M. Osteen & Michael I. Cannon, *Continuing Medical Education: Unabated Debate*, 268 JAMA 1118, 1119 (1992) (noting that "several companies withdrew all support of accredited CME until the rules became clear, lest they be held in violation by the FDA").

[98] *See generally Bristol-Myers Squibb's Distribution of Medical Textbook Excerpts Will Be Discussed*, THE PINK SHEET (July 13, 1992). In May 1991, Bristol-Myers Squibb entered into an agreement with the agency to preclear all promotional materials relating to oncology products for two years. *Id.*

[99] *Id.* at 2.

[100] *Id.* at 4.

[101] *Id.*

statement," in the Federal Register and requested public comment.[102] Recognizing "the need for industry-supported dissemination of current scientific information" and "the need for industry-supported scientific and educational activities," FDA said that it had historically permitted manufacturers to provide financial support for activities involving the provision of scientific information to health care practitioners.[103] The one limitation: financial support could be the only way in which the activity was not "independent" from the manufacturer's "promotional influence."[104] Specifically, FDA explained:

> Scientific and educational activities on therapeutic and diagnostic products (human and animal drugs, biological products, and medical devices) for health care professionals that are performed by or on behalf of the companies that market the products have traditionally been viewed by FDA as subject to regulation under the labeling and advertising provisions of the Federal Food, Drug, and Cosmetic Act (the act). To permit industry support for educational activities embracing a full exchange of scientific views, FDA has distinguished between those activities supported by companies that are otherwise independent from the promotional influence of the supporting company and those that are not. The agency does not seek to regulate activities that are independent and nonpromotional (i.e., that are not designed to promote the supporting company's products). Activities that fail to fall within this traditional safe harbor are not per se illegal, but they are subject to regulation.[105]

FDA did not make clear whether it intended to regulate activities that were supported by a manufacturer but not designed to promote the manufacturer's products.[106] Nor did it provide further detail as to the distinction between regulated promotional and non-promotional activities[107]

Industry raised concerns about numerous ambiguities in the draft policy statement, but nevertheless urged FDA to adopt the revised approach promptly to help address the decline in commercial funding of CME activities.[108] Industry also requested that FDA clarify whether it could rely on the draft policy statement "as guidance on FDA's position" until the policy could be issued in final form.[109] In February 1993, FDA announced that it was developing a policy to cover all industry-sponsored "enduring materials," loosely defined as materials of a lasting nature like books, audio, or video

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[102] Draft Policy Statement on Industry-Supported Scientific and Educational Activities, 57 Fed. Reg. 56,412, 56,412 (Nov. 27, 1992).

[103] *Id.*

[104] *Id.*

[105] *Id.*

[106] *See generally* Draft Policy Statement on Industry-Supported Scientific and Educational Activities, 57 Fed. Reg.

[107] *Id.*

[108] *FDA CME Policy Adoption Would Stem "Decline in Commercial Support,"* THE PINK SHEET, 2–3 (Mar. 22, 1993).

[109] *Id.* at 3.

tapes, and software.[110] Concerned that FDA would adopt the same restrictive approach to enduring materials that it had taken for scientific and educational activities, the medical community formed a task force under AMA auspices and developed its own proposed guidelines.[111] FDA met with the American Medical Writers Association and the American Medical Publishers to address the groups' concerns that FDA would establish a policy that "impede[s] . . . the free flow of information."[112]

In April 1993, two legal commentators objected to FDA's actions to preclude manufacturers from engaging in educational communications about off-label uses of their products.[113] According to one of these commentators, FDA's actions were so aggressive that "[c]ompanies and individuals who have nothing to do with the manufacture of drugs . . . have sharply criticized the agency's activities."[114] Other commentary also raised constitutional criticisms.[115] And, on October 22, 1993, the Washington Legal Foundation (WLF) submitted a citizen petition opposing the draft policy on First Amendment and other grounds.[116]

The WLF petition requested FDA remove the draft policy statement and adopt a new policy acknowledging that drug and medical device manufacturers are permitted to provide truthful medical information about off-label uses of approved drugs and medical devices.[117] The petition argued that any contrary policy would prove detrimental to patient care and would violate the First Amendment rights of physicians and consumers to receive information.[118] In April 1994, DDMAC set forth its views on responses to unsolicited requests in a letter to manufacturers.[119] The letter stated that DDMAC intended to revise the 1982 policy, but in the meantime:

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[110] *See* FDA to Target Scientific and Consumer Materials, FDA Advertising and Promotion Manual, Feb. 1993, at 1.

[111] *AMA Enduring Materials Draft Guidelines Calls for Full Disclosure*, THE PINK SHEET, 1 (Sept. 19, 1994).

[112] Citizen Petition Regarding the Food and Drug Administration's Policy on Promotion of Unapproved Uses of Approved Drugs and Devices; Request for Comment, 59 Fed. Reg. 59,820, 59,823 (Nov. 18, 1994).

[113] *See* Alan R. Bennett & Mark E. Boulding, *FDA Attempts to Regulate Medical Textbooks*, 28 MED. MARKETING & MEDIA 28 (1993).

[114] Mark E. Boulding, *The Statutory Basis for FDA Regulation of Scientific and Educational Information*, 4 J. PHARMACY & L. 123, 123 (1995) (footnote omitted).

[115] *See, e.g.*, Lars Noah & Barbara A. Noah, *Liberating Commercial Speech: Product Labeling Controls and the First Amendment*, 47 FLA. L. REV. 63 (1995); Charles J. Walsh & Alissa Pyrich, *FDA Efforts to Control the Flow of Information at Pharmaceutical Industry-Sponsored Medical Education Programs: A Regulatory Overdose*, 24 SETON HALL L. REV. 1325 (1994). One FDA employee published a defense of the agency's developing policies, noting that, although previous First Amendment challenges to FDA regulation had not succeeded, "interest in the constitutionality of the agency's approach has intensified in recent years in the context of the agency's much-publicized Draft Policy Statement on Industry-Supported Scientific and Educational Activities." *See* David G. Adams, *FDA Regulation of Communications on Pharmaceutical Products*, 24 SETON HALL L. REV. 1,399, 1,414 (1994) (author was then Director of the Policy Development and Coordination Staff in the Office of the Commissioner).

[116] Citizen Petition of Washington Legal Found. Regarding the Food and Drug Administration's Policy on Promotion of Unapproved Uses of Approved Drugs and Devices, Docket No. 92N-0434 (Oct. 22, 1993).

[117] *Id.* at 3.

[118] *Id.* at 11–13.

[119] U.S. FOOD & DRUG ADMIN., DIVISION OF DRUG MARKETING, ADVERTISING, AND COMMUNICATIONS (DDMAC), CURRENT ISSUES AND PROCEDURES 6 (Apr. 1994).

> [I]ndividual, nonpromotional responses by pharmaceutical companies to specific, unsolicited requests for information will not be considered as promotional labeling provided that: the sponsor maintains documentation concerning the nature of the request(s); and there is no pattern of repeated dissemination of materials or no evidence that such requests were solicited by the sponsor (e.g., preparation of material for routine dissemination).[120]

Like the 1982 policy, the 1994 document made clear that a manufacturer could not solicit a request for off-label information without subjecting its response to regulation as promotion.[121] The 1982 document spoke in terms of "precipitat[ing] or expressly encourag[ing]" requests; here, by contrast, DDMAC asserted that merely preparing material for routine dissemination could be evidence of solicitation. DDMAC dropped the recommendation that manufacturers include in their responses to unsolicited requests a statement of the approved indication and a reference to the full package insert. It also omitted any reference to suspending the unsolicited requests policy in response to perceived abuses.[122]

After receiving no final response from FDA to its October 22, 1993 petition, on June 13, 1994, WLF sued the agency in federal court on the ground that the draft policy violated the First Amendment.[123] On November 18, 1994, FDA published a notice, belatedly responding to the WLF citizen petition. The notice stated:

> Under current FDA policy companies may . . . disseminate information on unapproved uses in response to unsolicited requests for scientific information from health care professionals. Scientific departments within regulated companies generally maintain a large body of information on their products. When health care professionals request such information, companies can provide responsive, nonpromotional, balanced, scientific information, which may include information on unapproved uses, without subjecting their products to regulation based on the information. This policy permits companies to inform health care professionals about the general body of information available from the company.[124]

Under this version of the policy, a pharmaceutical manufacturer could provide off-label information to health care practitioners in response to their unsolicited requests.[125] The policy allowed practitioners access to the "large body" of scientific information available from medical affairs and other "[s]cientific departments" within

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[120] *Id.*

[121] *Id.*

[122] *Id.*

[123] Complaint, Washington Legal Found. v. Kessler, No. 1:94-cv-01306 (D.D.C. June 13, 1994) (ECF No. 1). FDA responded to the complaint, in part, by saying that the 1992 draft policy was not yet official and, therefore, could not be challenged. In its papers, FDA affirmed its position that "legitimate scientific exchange" among physicians was permissible, but again stated that promotion of off-label uses, including through CME and other ostensibly non-promotional media, was subject to agency regulation.

[124] Citizen Petition Regarding the Food and Drug Administration's Policy on Promotion of Unapproved Uses of Approved Drugs and Devices; Request for Comment, 59 Fed. Reg. 59,820, 59,823 (Nov. 18, 1994).

[125] *Id.*

regulated firms, even if that information concerned off-label uses of those firms' drug products.[126]

This articulation of the unsolicited requests policy is significant for a number of reasons. First, it contains none of the references to conduct that constitutes solicitation appearing in the 1982 and 1994 documents. Second, it makes clear that responses to unsolicited requests will not be regarded as "labeling," and that such responses will not subject the disseminating company's drugs to any kind of regulation (e.g., enforcement action under FDCA § 505(a)).[127] Third, it applies to responses by "companies"—not only medical affairs departments (although the policy contemplates that such departments will be the source of responsive information), but also others acting on behalf of the company—as long as the response is "responsive, nonpromotional, [and] balanced."[128]

The notice is also important for another reason. In contrast to the 1982 and April 1994 policy statements, which are informal documents issued by a component of one FDA center, the notice is a formal document representing the official view of the entire agency.[129] Because it is "[a] statement of policy or interpretation made in . . . a Federal Register Notice . . . , e.g., a notice to manufacturers . . . ," it binds FDA "unless subsequently repudiated by the agency or overruled by a court."[130]

Shortly after FDA published the notice, on December 2, 1994, DDMAC sent a letter to Burroughs Wellcome objecting to the company's dissemination of pre-approval information regarding an anti-seizure medication.[131] DDMAC took the position that the materials provided by the company exceeded the scope of the unsolicited requests policy because they contained conclusory statements about the safety and effectiveness of the drug. DDMAC emphasized that responses to requests must be "non-promotional, non-biased, scientific information."[132]

During this period, FDA also devoted substantial attention to finalizing its assertion of jurisdiction over tobacco products in an August 1995 proposed rule and an August 1996 final rule.[133] Central to FDA's position that its statutory authority included tobacco products was a novel theory of intended use crafted by Kessler and his Deputy,

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[126] *Id.*

[127] *Id.*

[128] *Id.*

[129] Any doubt that the 1982 and April 1994 policy statements had been overtaken by the November 1994 notice was dispelled on March 28, 1997, when FDA announced that it viewed the earlier documents as "obsolete." Prescription Drug Advertising and Promotional Labeling; Development and Use of FDA Guidance Documents; Request for Comments, 62 Fed. Reg. 14,912, 14,913–16 (Mar. 28, 1997). According to FDA, both documents would be incorporated into a new guidance document, entitled "Solicited and Unsolicited Requests for Information." *Id.* at 14,914, 14,916. This never happened.

[130] 21 C.F.R. § 10.85(d)(1); *see also id.* § 10.85(e) ("The Commissioner may not recommend legal action against a person or product with respect to an action taken in conformity with an advisory opinion which has not been amended or revoked.").

[131] *B-W's Full Detailing of Lamictal Must Await FDA Approval of Promotional Materials*, THE PINK SHEET, 1 (Feb. 20, 1995); Warning Letter to Burroughs Wellcome Co. re: Lamictal (lamotrigine) Tablets (Dec. 2, 1994).

[132] THE PINK SHEET, 7 (Feb. 20, 1995).

[133] *See* Regulations Restricting the Sale and Distribution of Cigarettes and Smokeless Tobacco Products to Protect Children and Adolescents, 60 Fed. Reg. 41,314 (proposed Aug. 11, 1995) (proposed rule); Regulations Restricting the Sale and Distribution of Cigarettes and Smokeless Tobacco to Protect Children and Adolescents, 61 Fed. Reg. 44,396 (Aug. 28, 1996) (final rule).

Bill Schultz.[134] According to this theory, the "intended use" of a product (including a tobacco product), and hence FDA's statutory entitlement to regulate it as a drug or as a device, was not established by the manufacturer claims made for it.[135] Instead, Kessler and Schultz argued, FDA could permissibly examine internal company documents (which, they contended, revealed the "subjective intent" of the manufacturer), the foreseeability of tobacco's pharmacological effects, and the actual use of the product by consumers for those effects.[136] In essence, FDA's novel theory, developed specifically to enable the agency to assert jurisdiction over tobacco products, was that intended use could be "evidenced."[137] As discussed further below, FDA would use this theory to regulate manufacturer dissemination of off-label information and to defend its approach in the *WLF* litigation.

Congress became interested in FDA's increasingly restrictive approach to off-label information in late 1995. At a hearing on November 15, Representative Barton (R-Tex.) announced that a House of Representatives oversight subcommittee would consider FDA regulation of off-label promotion and agency "censorship."[138] Congress later sought to address the off-label issue through legislation. The resulting provision—Section 401 of the Food and Drug Administration Modernization Act of 1997 (FDAMA)—is discussed further below.[139] On December 6, 1995, FDA published two draft guidance documents entitled "Guidance to Industry on Dissemination of Reprints of Certain Published, Original Data," and "Guidance for Industry-Funded Dissemination of Reference Texts."[140] The guidance documents described the circumstances in which FDA would exercise enforcement discretion to permit manufacturers to disseminate scientific and medical journal article reprints and reference texts containing off-label information to health care professionals. FDA's unstated premise was that it had legal authority to regulate these materials, despite the agency's previous position that "dissemination" was unregulated.[141] In August 1996, DDMAC issued a letter to Zeneca objecting to a packet of information, prepared to respond to unsolicited requests, regarding the sustained-release morphine product

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[134] DAVID KESSLER, A QUESTION OF INTENT: A GREAT AMERICAN BATTLE WITH A DEADLY INDUSTRY 270–72 (2001). Schultz, by then Deputy Assistant Attorney General, argued the *WLF* case for FDA in the Court of Appeals in January 2000—three months before the Supreme Court invalidated the tobacco regulations in the *Brown & Williamson* case, discussed further below.

[135] *Id.* at 270–72.

[136] *See, e.g.*, 60 Fed. Reg. 41,314, 41,471–82; KESSLER, *supra* note 134, at 270–72. Although the Supreme Court resolved the *Brown & Williamson* case without needing to address "intended use," the Fourth Circuit in the case below had observed that "no court has ever found that a product is 'intended for use' or 'intended to affect' within the meaning of the [FDCA] absent manufacturer claims as to that product's use." Brown & Williamson Tobacco Corp. v. FDA, 153 F.3d 155, 163 (4th Cir. 1998) (internal quotation omitted), *aff'd*, 529 U.S. 120 (2000).

[137] Richard M. Cooper, *The WLF Case Thus Far: Not With a Bang, But a Whimper*, 55 FOOD & DRUG L.J. 477, 484–86 (2000).

[138] *Journal Reprints*, *supra* note 89 (citing THE PINK SHEET (Nov 20, 1995)).

[139] *See infra* note 153.

[140] Advertising and Promotion; Draft Guidances, 60 Fed. Reg. 62,471 (Dec. 6, 1995); Advertising and Promotion; Draft Guidances; Republication, 60 Fed. Reg. 63,384 (Dec. 8, 1995) (republished due to "inadvertently omitted" text); THE PINK SHEET, (Nov. 20, 1995); *see also Journal Reprints*, *supra* note 89, at 3.

[141] *See* Advertising and Promotion; Draft Guidances, 60 Fed. Reg. at 62,471.

Kadian, distributed prior to the July 3 approval date.[142] DDMAC followed the same approach it took in its December 1994 warning letter to Burroughs Wellcome. The Zeneca letter asserted that the packet constituted "pre-approval promotion of the product" because of information contained in the packet relating to its proposed indication, dosing guidelines, and comparative trials implying efficacy of Kadian. The letter explained that information provided in response to unsolicited requests should be "narrowly tailored" and "should not draw conclusions about the product."[143]

In September 1996, FDA addressed the scientific exchange regulation at 21 C.F.R. § 312.7(a) in a notice announcing a public meeting to discuss issues related to the promotion of FDA-regulated medical products on the Internet.[144] The notice recognized the usefulness of information about off-label uses in the context of scientific exchange and implied that the test for whether a communication is promotional is whether it is intended for promotional purposes.

> Several companies that market FDA-regulated medical products have inquired about the extent to which information regarding investigational products or investigational uses of products can be placed on their website. Currently, FDA regulations prohibit representing "* * * in a promotional context that an investigational new drug is safe or effective for the purposes for which it is under investigation * * *" and prohibits the "* * * commercialization of the drug before it is approved for commercial distribution." (See 21 CFR 312.7(a).) A similar regulation applies to investigational devices. (See 21 CFR 812.7.) Many companies have placed on their website information intended for stockholders or potential stockholders, which often contain information about products or uses under investigation. In some cases, however, it is difficult for the Internet user to distinguish whether the presentation of this information is intended for economic or promotional purposes. The agency recognizes that information about investigational products and uses can be useful in the context of scientific exchange. FDA has the following questions regarding investigational product information:
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> To what extent should information about investigational products or investigational uses be presented on a sponsoring company's website? Is there a way to distinguish between the presentation of this information for economic, educational, or promotional purposes?[145]

On October 8, 1996, FDA published final versions of the two draft guidance documents first published in December 1995, "Guidance to Industry on Dissemination of Reprints of Certain Published, Original Data," and "Guidance for Industry-Funded Dissemination of Reference Texts," with only one change.[146] In the preamble

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[142] *Boehringer Ingelheim Atrovent Promotions of "Fast" Onset Claim Challenged by FDA; Seven Firms Have Been Cited By Agency for Asthma/Allergy Promotions*, THE PINK SHEET, 6 (Dec. 9, 1996).

[143] *Id.*

[144] Promotion of FDA-Regulated Medical Products on the Internet; Notice of Public Meeting, 61 Fed. Reg. 48,707 (Sept. 16, 1996).

[145] *Id.* at 48,709.

[146] *See* Advertising and Promotion; Guidances, 61 Fed. Reg. 52,800, 52,800 (Oct. 8, 1996). The final version of "Guidance to Industry on Dissemination of Reprints of Certain Published Original Data" was

accompanying the final guidance documents on reprints and reference texts, FDA referred to "the need for an exchange of reliable scientific data and information within the health care community."[147] The agency did not cite § 312.7(a).

On March 28, 1997, FDA published a Federal Register notice proposing new guidance documents in the promotion area (e.g., on internet promotion) and listing the prescription drug advertising and promotional labeling policy statements it had issued since 1970, identifying those it viewed as obsolete.[148] Included among the obsolete policy statements was the April 1982 document on responses to unsolicited requests.[149] The November 1994 Federal Register notice therefore represented FDA policy with respect to manufacturer responses to unsolicited requests.

In the wake of the notice, confusion persisted over what, exactly, manufacturers were permitted to communicate about off-label uses of their products. At a hearing before the health subcommittee of the House Commerce Committee on April 23, 1997, FDA Deputy Commissioner for Policy William Schultz stated: "It's sort of a line between dissemination and promotion, and what we say to the drug companies is if you do the work you get to promote and sell your product for that new use, but if you don't do the work then you don't get to promote your product."[150] Schultz thus suggested that "dissemination," in contrast to promotion, of off-label information might still be outside FDA's regulatory authority. That DDMAC continued to send warning and untitled letters to manufacturers objecting to off-label promotion—but not "dissemination" of off-label information—reinforced this view.[151]

Not surprisingly then, FDA continued to acknowledge the unsolicited requests policy, which had always been described as permitting limited, non-promotional communication by manufacturers about off-label uses. In June 1997, at a Drug Information Association (DIA) meeting, the Director of the Center for Drug Evaluation and Research (CDER) delivered remarks on off-label information dissemination, which included the following passage:

> [P]rescribers and other parties may obtain, upon request, information on off-label uses from the pharmaceutical firms or other medical products

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identical to the draft. One additional circumstance for dissemination, regarding product promotion, was added to the final version of "Guidance for Industry-Funded Dissemination of Reference Texts."

[147] *Id.* The full passage states: "The agency received several comments claiming that the guidance on dissemination of certain reprints does not go far enough, arguing that companies should be permitted to disseminate any article they choose, regardless of what information is discussed in the article or whether the information is consistent with the approved product labeling. The agency also received several comments that gave specific suggestions of the types of articles that should be permitted under a policy with a broader scope (e.g., all peer-reviewed articles, technical reports). FDA believes that the guidances that are the subject of this notice strike the proper balance between the need for an exchange of reliable scientific data and information within the health care community, and the statutory requirements that prohibit companies from promoting products for unapproved uses. However, the agency will continue to evaluate its policies related to the advertising and promotion of FDA-regulated products, and these guidances are just one part of its policy in this area." *Id.*

[148] *See* Prescription Drug Advertising and Promotional Labeling; Development and Use of FDA Guidance Documents; Request for Comments, 62 Fed. Reg. 14,912, 14,912 (Mar. 28, 1997).

[149] According to FDA, both documents would be incorporated into a new guidance document, entitled "Solicited and Unsolicited Requests for Information." *Id.* at 14, 916. This never happened.

[150] THE PINK SHEET, 8 (Apr. 28, 1997).

[151] *See, e.g.*, *Amersham Myoview Cited For Off-Label Promotions in Aug. 21 FDA Warning Letter*, THE PINK SHEET, 1–2 (Aug. 25, 1997).

> sponsors. Under the FDA's "policy on solicited information," physicians, pharmacists, and other interested parties may solicit information from the manufacturers, including information on off-label uses. Recognizing that off-label uses can be important and appropriate in medical practice, and that practitioners may need to get such information in a specific situation, the agency does not bar them from requesting and receiving that information, provided it is not presented in a promotional context.[152]

In November 1997, Congress amended the FDCA expressly to allow manufacturer dissemination of peer-reviewed journal articles concerning the "safety, effectiveness, or benefits of a use not described in the approved labeling" in specified circumstances.[153] Under Section 401 of FDAMA, these conditions included, among other things: 1) the disseminated information must be unabridged, must not be false or misleading, and must not pose a significant risk to public health; 2) the company must submit an advance copy of the information to be disseminated to FDA along with any clinical trial information and reports of clinical experience; and 3) the disseminated information must include a prominently displayed statement disclosing, among other things, that the material concerns a use for which the drug has not approved by FDA.[154] The relevant provisions, accompanying legislative history, and implementing regulations share common themes: FDA's existing policy on unsolicited requests remained the same, and whatever authority FDA had before the legislation to restrict manufacturer dissemination of off-label information in response to unsolicited requests was not affected by the new rules governing proactive dissemination of such information. Most significantly, FDAMA provided a six-month window for a manufacturer to disseminate information under the specified conditions before the company had to submit an application for the new use.[155] The relationship of FDAMA § 401 to the unsolicited requests policy was not clear. Section 401 of FDAMA provided:

> (a) UNSOLICITED REQUEST.—Nothing in section 551 [describing the circumstances in which a manufacturer is permitted to disseminate off-label information] shall be construed as prohibiting a manufacturer from disseminating information in response to an unsolicited request from a health care practitioner.[156]

According to the House report accompanying this provision:

> The Committee wants to emphasize that current FDA policies that encourage scientific exchange are not being modified by section 745 [describing the requirements a manufacturer must meet in order to disseminate off-label information]. At the same time, insofar as the Secretary may currently have authority under other sections of the FFDCA to restrict a manufacturer's dissemination of information in

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[152] Janet Woodcock, *A Shift in the Regulatory Approach*, 32 DRUG INFO. J. 367, 368 (1998) (remarks at the DIA 33rd Annual Meeting, June 22–26, 1997, Montreal, Canada).

[153] Food And Drug Modernization Act of 1997, Pub. L. No. 105-115, § 401, 111 Stat. 2296 (codified at 21 U.S.C. § 360aaa).

[154] 21 U.S.C. § 360aaa-1 (1988).

[155] 21 U.S.C. § 360aaa-3 (1998).

[156] 21 U.S.C. § 360aaa-6 (1998).

> response to an unsolicited request from a health care practitioner, nothing in section 745 is intended to change or limit that authority.[157]

It was also not understood how 21 C.F.R. § 312.7 might be affected by the new legislation. One possible interpretation was that manufacturers could continue to engage in such exchange, and that FDAMA § 401 created yet another avenue for off-label information to reach physicians and patients. At least one commentator interpreted FDAMA § 401 as authorizing manufacturers "to engage in the off-label marketing and promotion of the drugs they produce," albeit subject to limitations spelled out in the statute.[158]

In December 1997, the agency finalized the guidance on industry-supported scientific and educational activities (ISSEA).[159] The guidance identified twelve factors the agency would consider in determining whether a manufacturer, through its support of scientific and educational activities, had created a new use for a drug for which approval would be required. The guidance thus appeared to contemplate that FDA would not automatically regulate manufacturer-supported scientific and educational programs as promotion. Companies had to engage in a fact-intensive case-by-case analysis in view of the factors set forth in the guidance, but an activity that qualified for the safe harbor was deemed outside the scope of FDA's authority.

In the preamble accompanying the final guidance on ISSEA, FDA explained that § 312.7(a) reflects "the distinction between the concepts of promotion/commercialization and industry-supported scientific exchange."[160] FDA seemed to say that a manufacturer could support scientific exchange programs as long as the only tie between the manufacturer and the provider is the provision of financial support:

> The comments contended that the draft policy statement seems to subject company-controlled scientific exchange to regulation because it is not an independent activity. They contended that appropriate company-controlled scientific exchange should be expressly exempted from regulation in the policy.
>
> This final guidance seeks to clarify the distinction between the concepts of promotion/commercialization and industry-supported scientific exchange set forth in §§ 312.7(a) (human drugs) and 511.1(b)(8)(iv) (animal drugs). Programs supported by companies that are not otherwise independent scientific or educational activities are subject to regulation as product promotion/commercialization.[161]

By finalizing the third of its three off-label guidance documents, on ISSEA, the FDA did not quiet its critics. Commentators noted the tension between FDA's

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[157] H.R. Rep. No. 105-310, at 62, 63 (1997).

[158] Steven R. Salbu, *Off-Label Use, Prescription, and Marketing of FDA-Approved Drugs: An Assessment of Legislative and Regulatory Policy*, 51 FLA. L. REV. 181, 31 (1999).

[159] *See* Final Guidance on Industry-Supported Scientific and Educational Activities, 62 Fed. Reg. 64,074 (Dec. 3, 1997).

[160] *Id.* at 64,083.

[161] *Id.*

approach and the First Amendment.[162] One analysis contended that the ISSEA guidance "is contrary to the spirit, if not the letter, of" 21 C.F.R. § 312.7.[163] "It is confusing," the authors asserted, for FDA to "simultaneously to recognize the need for pre-approval dissemination of scientific information in one regulation, but to assert that dissemination of such information is sanctionable in the rules on industry support for educational symposia."[164]

4. The WLF *Litigation*

Several months after enactment of FDAMA, WLF won a major victory in its lawsuit against FDA. On July 30, 1998, the United States District Court for the District of Columbia enjoined FDA from seeking to limit any pharmaceutical manufacturer's ability to: 1) disseminate to health care practitioners any off-label article previously published in a bona fide peer-reviewed professional journal; 2) disseminate to health care practitioners any off-label reference textbook (or part of a reference textbook) published by a bona fide independent publisher and otherwise generally available for sale in bookstores or other distribution channels where similar books are normally available; or 3) suggest content or speakers to an independent program provider in connection with a CME program or other symposium, regardless of whether off-label uses are to be discussed.[165] This decision became known as WLF I.

The court's order in *WLF I* did not provide conclusive direction. It was unclear whether the court's order applied to Section 401 of FDAMA, which was set to go into effect within several months after the court's order. FDA immediately moved to amend the order, asking the court to declare that FDAMA was outside its scope.[166] In November 1998, FDA issued regulations implementing FDAMA Section 401, which took an approach similar to the House report in interpreting the impact of the statute on FDA's authority. In the preamble accompanying the final regulations, FDA stated that it did not construe the FDAMA provision as providing a "specific legal authorization for manufacturers to provide off-label use information to health care

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[162] *See, e.g.*, Edmund Polubinski III, *Closing the Channels of Communication: A First Amendment Analysis of the FDA's Policy on Manufacturer Promotion of "Off-Label" Use*, 83 VA. L. REV. 991, 994 (1997) (arguing that FDA's guidance documents are unconstitutional).

[163] I. Scott Bass, Paul E. Kalb & Bradford A. Berenson, *Off-Label Promotion: Is FDA's Final Guidance on Industry-Supported Scientific and Educational Programs Enforceable?*, 53 FOOD & DRUG L.J. 193, 201 (1998).

[164] *Id.*

[165] Washington Legal Found. v. Friedman, 13 F. Supp. 2d 51, 74–75 (D.D.C. 1998), *vacated in part*, 202 F.3d 331 (2000) ("*WLF I*"). The court determined that the dissemination of information by drug companies constituted commercial speech, and, thus, it applied the four-prong test established in *Central Hudson Gas & Elec. Corp. v. Pub. Serv. Comm'n of New York*, 447 U.S. 557, 564–66 (1980), to determine whether FDA's restrictions were unconstitutional. *WLF I*, 13 F. Supp. at 65–74. The court concluded that FDA's restrictions were unconstitutional under the final prong of the *Central Hudson* test because they were "more extensive than necessary to serve the asserted government interest and that they unduly burden important speech." *Id.* at 74. The district court later clarified that the injunction applied only to off-label uses of approved drugs and not to drugs that have not received FDA approval for any use. Washington Legal Found. v. Friedman, 36 F. Supp. 2d 16, 17–18 (D.D.C. 1999), *vacated in part*, 202 F.3d 331 (2000).

[166] Washington Legal Found. v. Henney, 56 F. Supp. 2d 81, 82 (D.D.C. 1999), *vacated in part*, 202 F.3d 331 (2000) ("*WLF II*") (denying FDA's motion to amend the July 30, 1998 Order insofar as it seeks to exclude the FDAMA from the July 20, 1998 Order's scope).

practitioners in response to an unsolicited request . . . ."[167] It appears FDA wished to regard the unsolicited requests policy as an exercise in prosecutorial discretion rather than a statutory limitation on the agency's authority.

On July 28, 1999, the United States District Court for the District of Columbia ruled that FDAMA was unconstitutional in that it perpetuated the underlying policies held unconstitutional in *WLF I*.[168] Until the July 1999 decision ruling on FDA's motion, it had been unresolved whether FDAMA's restrictive procedure for disseminating off-label information violated the First Amendment. Under *WLF II*, the court amended the *WLF I* order "to explicitly declare unconstitutional and unenforceable the FDAMA and its implementing regulations."[169] FDA appealed the decision, "contending that the district court erred in concluding that the FDAMA and the CME Guidance are unconstitutional."[170] Because of the pending appeal, the district court's July 1999 decision in *WLF II* did not resolve the drug industry's uncertainty. It did, however, cast considerable doubt on FDA's regulatory authority over manufacturers' off-label communications.[171]

On February 11, 2000, the United States Court of Appeals for the District of Columbia Circuit issued its opinion in *WLF III*. The court did not reach the First Amendment issue because WLF stated that it no longer had a constitutional objection to FDAMA or the CME guidance in light of FDA's assertion during oral argument that neither the guidance nor FDAMA "provides the FDA with independent authority to regulate manufacturer speech."[172] FDA asserted that FDAMA and the CME Guidance "established nothing more than a 'safe harbor' ensuring that certain forms of conduct would not be used against manufacturers in misbranding and 'intended use' enforcement actions based on pre-existing legislative authority."[173] Because FDA's assertion eliminated the narrow constitutional controversy that was the subject of the appeal, the court dismissed the action and vacated the district court's decisions and injunctions "insofar as they declare the FDAMA and the CME Guidance unconstitutional."[174] The appellate court's opinion purported to leave intact part of the district court's injunction and did not take issue with its First Amendment analysis, but, on remand, the district court found that nothing in the order survived the appellate analysis.[175]

The court's decision in *WLF III* "has been called unclear, and both parties claimed victory after hearing the ruling."[176] The court stated that FDA could use "both types of

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[167] Dissemination of Information on Unapproved/New Uses for Marketed Drugs, Biologics, and Devices, 63 Fed. Reg. 64,556, 64,558 (Nov. 20, 1998) (codified at 21 C.F.R. § 99.1(b)) ("This part does not apply to a manufacturer's dissemination of information that responds to a health care practitioner's unsolicited request.").

[168] *WLF II*, 56 F.Supp.2d at 84.

[169] *Id.* at 87.

[170] Washington Legal Found. v. Henney, 202 F.3d 331, 335 (D.C. Cir. 2000) ("*WLF III*").

[171] *See, e.g.*, Jeffrey N. Gibbs, *First Amendment Limits on Regulating Information: An Initial Reaction to the Washington Legal Foundation Case*, 53 FOOD & DRUG L.J. 597, 600 (1998).

[172] *WLF III*, 202 F.3d at 336.

[173] *Id.* at 335.

[174] *Id.* at 337.

[175] Washington Legal Found. v. Henney, 128 F. Supp. 2d 11, 15 (D.D.C. 2000).

[176] Richard C. Ascroft, *The Impact of the Washington Legal Foundation Cases on Pharmaceutical Manufacturer Practices in the United States*, 34 IND. L. REV. 95, 105 (2000) (citations omitted). "It is not

arguably promotional conduct as evidence in a misbranding or 'intended use' enforcement action,"[177] yet it mentioned that a manufacturer "may still argue that the FDA's use of a manufacturer's promotion of off-label uses as evidence in a particular enforcement action violates the First Amendment."[178] After *WLF III*, drug companies were (and remained) very much uncertain as to what types of communication constitute "promotional conduct" that could be used as "evidence in a misbranding or 'intended use' enforcement action," and whether the use of such conduct as evidence in such an action would be unconstitutional.[179] One commentator observed that the *WLF III* "decision is unclear at best. . . . Left open is whether the FDA's ability to utilize other provisions of the FDCA to limit the dissemination of off-label information and bring enforcement actions against manufacturers could successfully be challenged as unconstitutional."[180]

After the Court of Appeals ruling, on March 16, 2000, FDA issued a Federal Register document setting forth the agency's current stance on the activities covered by the three off-label guidance documents.[181] In the notice, FDA reiterated the "safe harbor" interpretation that it had first advanced in the appellate court.[182] Although the ISSEA guidance lacked the force and effect of law, FDA stated that the agency would look to its factors in determining whether a particular activity could be used as "evidence" of a new intended use.[183] The agency stated that it viewed the reprints and textbooks guidances as superseded by Section 401 of FDAMA. FDA also said, however, that it believed the ISSEA guidance was not affected by FDAMA.

The notice did not clarify the regulatory environment. One member of the bar characterized off-label information dissemination as "a very confused area" and said that the *WLF* decision "muddies the water considerably."[184] An FDA official noted at an advisory committee meeting in July 2000 that the question remained largely unsettled.[185] WLF went back to court, this time seeking clarification of the district court's order and revocation of the March 16 notice.

On March 21, 2000, the United States Supreme Court handed down its decision in *FDA v. Brown & Williamson*, 529 U.S. 120 (2000). In *Brown & Williamson*, the

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clear whether this is a return to the situation that existed before or whether FDA has a burden to show more than dissemination of information to bring action against a company." *Id*. at 96 n.5 (citing Lisa Richwine, *USA: Court Dismisses FDA Appeal on Drug Promotion*, REUTERS ENG. NEWS SERV. (Feb. 11, 2000)).

[177] *WLF III*, 202 F.3d at 336.

[178] *Id*. at 336 n. 6.

[179] Ascroft, *supra* note 176, at 106 (citations omitted).

[180] *Id.*; *see also* Cooper, *supra* note 137, at 477 ("The recent D.C. Circuit decision in the case has created much confusion about the state of the applicable law.").

[181] *See* Decision in Washington Legal Foundation v. Henney, 65 Fed. Reg. 14,286 (Mar. 16, 2000).

[182] *Id.* at 14,287.

[183] *Id.*

[184] *WLF Confusion Benefits FDA by Deterring Dissemination, Bennett Says*, THE PINK SHEET, 3 (Mar. 20, 2000) (quoting longtime FDA practitioner Alan Bennett); *see also* THE PINK SHEET, 23 (Apr. 10, 2000) (Pharmacia attorney commenting on uncertainty of enforcement actions following the Court of Appeals decision).

[185] *Off-Label HIV Regimen Data Should be Provided to Doctors by FDA - Cmte.*, THE PINK SHEET, 1 (July 31, 2000) (FDA Antiviral Drugs Division Director Heidi Jolson, M.D., noting that the courts are still debating the issue of off-label dissemination and that they have ruled that FDA cannot prohibit companies from distributing information that is publicly available).

Supreme Court invalidated FDA's tobacco regulations on the ground that the presence of several tobacco-specific statutes demonstrated that Congress had not given the agency authority over those products. Although the Supreme Court did not decide the case with reference to FDA's "intended use" theory, which defined intended use to include tobacco product manufacturers' internal company documents, the known pharmacological effects of nicotine in tobacco products, and consumer use of such products for those effects, it did strike down the regulations in their entirety, implicitly rejecting the agency's approach. Moreover, earlier in the case, the Fourth Circuit had observed that "no court has ever found that a product is 'intended for use' or 'intended to affect' within the meaning of the [FDCA] absent manufacturer claims as to that product's use."[186] Because of the similarity between FDA's intended use theories in the *WLF* and tobacco cases, FDA's loss in *Brown & Williamson* further hinted at vulnerability in the agency's treatment of off-label information dissemination by manufacturers.[187]

On November 30, 2000, the district court judge in the *WLF* litigation declined to grant WLF's requested relief (clarification of the district court's order and revocation of the March 16 notice), but also castigated the agency for its failure to resolve the issue: "After six years' worth of briefs, motions, opinions, congressional acts and more opinions, the issue remains 100% unresolved, and the country's drug manufacturers are still without clear guidance as to the permissibility of this conduct."[188]

On May 23, 2001, WLF submitted a citizen petition asking FDA to withdraw the March 16 notice and in its place "issue a policy statement that indicates FDA's willingness to adhere" to the district court decision.[189] Under WLF's requested "policy statement," manufacturers would not be subject to FDA enforcement action for

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[186] *See* Brown & Williamson Tobacco Corp. v. FDA, 153 F.3d 155, 163 (4th Cir. 1998) (internal citation omitted), *aff'd*, 529 U.S. 120 (2000).

[187] To defend its treatment of off-label information dissemination by manufacturers in *WLF*, FDA used the novel theory of intended use developed specifically for tobacco. *See Brown*, 153 F.3d at 160–61. As one prominent commentator, former FDA Chief Counsel Rich Cooper, explained:

> FDA presented to the court of appeals [in *WLF*] a new theory of intended use . . . . For decades, it generally has been understood that intended uses are established by manufacturer statements. It is not that intended uses are established by events in the minds of manufacturers (whatever those may be) and that the statements are merely evidence of what has occurred in those minds; rather, the statements create the intended uses, and the minds (and evidence of what has occurred in those minds) are irrelevant.

See Cooper, *supra* note 137, at 484–86. Not so, says FDA. Manufacturer statements are merely evidence of the manufacturer's subjective intent (which can also be shown by other kinds of evidence). *Id.* So, under its legal theory, FDA can prove an (off-label) intended use by means other than manufacturer statements in the marketplace. *Id.* FDA has similarly applied this theory of intended use to the so-called "pediatric rule" rulemaking proceeding, where FDA asserted that "'[i]ntended uses' encompass more than the uses explicitly included in the manufacturer's proposed labeling" and that "FDA may consider both the uses for which it is expressly labeled and those for which the drug is commonly used." Regulations Requiring Manufacturers to Assess the Safety and Effectiveness of New Drugs and Biological Products in Pediatric Patients, 63 Fed. Reg. 66,632, 66,658 (Dec. 2, 1998) (to be codified at 21 C.F.R. pts 201, 312, 314, 601). In 2002, the United States District Court for the District of Columbia invalidated the pediatric rule, noting that "[i]f 21 U.S.C. § 355(d) truly gave the FDA the authority that it claims, the door would be open to FDA's regulation of all off-label uses, based solely on the manufacturer's knowledge that those uses are common-place." Ass'n of Am. Physicians & Surgeons, Inc. v. FDA, 226 F. Supp. 2d 204, 218 (D.D.C. 2002).

[188] Washington Legal Found. v. Henney, 128 F. Supp. 2d 11, 15 (D.D.C. 2000).

[189] *See* Letter from Daniel J. Popeo & Richard A. Samp, WLF, to Dockets Management Branch, May 23, 2001.

disseminating enduring materials that contain truthful information about off-label uses or for providing support for scientific and educational activities "along the lines outlined by the district court as constituting protected First Amendment activities."[190] In the petition, WLF explained that FDA had disregarded the district court's First Amendment rulings in both the March 16 notice and in enforcement letters sent to manufacturers. The petition also pointedly remarked on FDA's losses in other First Amendment cases: "Suffice to say that FDA has been on an extended losing streak in the courts in its efforts to resist First Amendment limitations on its enforcement activities."[191]

On January 28, 2002, FDA denied the WLF petition, defending the March 16 notice as entirely proper and consistent with the parties' positions in the *WLF* litigation.[192] At the same time, the agency "recognize[d] that in enforcing the [FDCA] . . . , it must respect the rights guaranteed by the First Amendment." FDA reiterated that distributing reprints or sponsoring CME in a manner that does not accord with the "safe harbors" established by FDAMA or the CME guidance, respectively, could serve as "evidence of [the manufacturer's] intent[.]"[193] The response also stated, however, that dissemination of journal reprints or sponsorship of CME would by themselves probably not trigger FDA enforcement action.[194] FDA's response did not bring clarity to the regulatory environment. According to the trade press, WLF itself "expressed disappointment with the decision, maintaining it does little to clear up manufacturer uncertainty over the FDA's enforcement practices."[195]

If the *WLF* litigation and *Brown & Williamson* cases suggested the FDA's off-label policies could be challenged on First Amendment grounds, a 2002 decision confirmed as much. In April 2002, the Supreme Court held in *Thompson v. Western States Medical Center*, that FDA's regulations under FDAMA, which prohibits the marketing of compounded drugs, impermissibly restricted commercial speech.[196] As noted in one analysis:

> After *Western States*, FDA can no longer assert that its use of speech as a proxy for conduct is exempt from First Amendment scrutiny. Its use of speech to determine when a regulated drug or device will be treated as "new" for purposes of approval requirements such as 21 U.S.C. § 355(a), or as "misbranded" for purposes of enforcing 21 U.S.C. § 352(f)—rather

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[190] *See id.*

[191] *Id.* at 27; *see also, e.g.*, Pearson v. Shalala, 164 F.3d 650 (D.C. Cir. 1999) (holding that the First Amendment imposes strict limitations on FDA's power to restrict health claims made by manufacturers of dietary supplements, even when the claims are made on the product label); Pearson v. Shalala, 130 F. Supp. 2d 105, 112 (D.D.C. 2001) ("[I]t is clear that the FDA simply failed to comply with the [First Amendment] guidelines outlined in *Pearson [I]*. Indeed, the agency appears to have at best, misunderstood, and at worst, deliberately ignored, highly relevant portions of the Court of Appeals Opinion."); W. States Med. Ctr. v. Shalala, 238 F.3d 1090 (9th Cir. 2001) (holding that a FDAMA provision that restricts pharmacists from advertising the availability of compounded drugs cannot survive the final two prongs of the *Central Hudson* test and thus violates the First Amendment).

[192] Letter from Margaret M. Dotzel, Assoc. Comm'r for Policy, Public Health Service, U.S. Food & Drug Admin., to Daniel J. Popeo & Richard A. Samp, WLF (Jan. 28, 2002).

[193] *Id.* at 1.

[194] *Id.* at 6. As a technical, legal matter, the letter has no legal force, per 21 C.F.R. § 10.85(k).

[195] THE GRAY SHEET, 5 (Feb. 4, 2002).

[196] 535 U.S. 357, 360 (2002).

> than some other benchmark—must survive exacting First Amendment standards.[197]

Shortly after the Court's decision in *Western States*, in May 2002, FDA published a notice requesting comments from the public to ensure that its regulations, guidances, policies, and practices continue to comply with the governing First Amendment case law, particularly the Supreme Court's decision in *Western States*.[198] The notice asked for comments on "the extent of FDA's ability to regulate speech concerning off-label uses."[199] The agency itself thus signaled, if not uncertainty, then at least a willingness to entertain alternative views.

In reporting on the notice, one trade press outlet observed: "Since the WLF case, FDA has avoided a clear declaration of limits on off-label promotion, which some sponsors feel has increased confusion about where the boundaries are."[200] It noted, further, that FDA's response to the most recent WLF citizen petition "affirmed" the agency's policy of generally not taking enforcement action against manufacturers who merely distribute off-label reprints.[201] The trade publication characterized the May 16 notice as evidence that FDA was reconsidering its authority over speech concerning off-label uses.[202]

FDA's interpretation of intended use, originally developed to regulate tobacco in 1995 and later used in the *WLF* cases, was again the subject of judicial analysis in October 2002. Although the tobacco litigation concluded without the Supreme Court passing on FDA's novel intended use theory, a challenge to an unrelated rule[203] yielded a merits opinion. In 2002, the United States District Court for the District of Columbia invalidated FDA's final rule on pediatric drugs.[204] According to the court, FDA's position in the litigation hinged on the FDCA definition of "new drug," pursuant to which the new drug approval requirement applied only with respect to the conditions "prescribed, recommended, or suggested in the proposed labeling thereof."[205] The agency contended that pediatric use was "suggested" within the meaning of the new drug definition because drugs intended for adult use are routinely used in pediatric patients.[206] Describing this argument as "unfortunate," the court rejected FDA's position:

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[197] A. Elizabeth Blackwell & James M. Beck, *Drug Manufacturers' First Amendment Right to Advertise and Promote Their Products for Off-Label Use: Avoiding a Pyrrhic Victory*, 58 FOOD & DRUG L.J. 439, 445–46 (2003).

[198] Request for Comment on First Amendment Issues, 67 Fed. Reg. 34,942, 34,943 (May 16, 2002).

[199] *Id.* at 34,944.

[200] THE PINK SHEET (May 20, 2002).

[201] *Id.*

[202] *Id*. Another example of FDA action to reexamine its policies on off-label information dissemination is Commissioner Mark B. McClellan's efforts to establish a working group on the issue. The group never formally formed, reportedly because of internal agency opposition. FDA WEEK (Feb. 11, 2005).

[203] *See* Regulations Requiring Manufacturers to Assess the Safety and Effectiveness of New Drugs and Biological Products in Pediatric Patients, 62 Fed. Reg. 43,900, 1997 WL 463874 (Aug. 15, 1997).

[204] Ass'n of Am. Physicians & Surgeons, Inc. v. FDA, 226 F. Supp. 2d 204 (D.D.C. 2002).

[205] *Id.* at 214 (citing 21 U.S.C. § 355(d)(1)); Regulations Requiring Manufacturers to Assess the Safety and Effectiveness of New Drugs and Biological Products in Pediatric Patients, 62 Fed. Reg. at 43,908 (citations and internal quotation marks omitted).

[206] *Ass'n of Am. Physicians & Surgeons, Inc.*, 226 F. Supp. 2d at 215.

> If 21 U.S.C. § 355(d) truly gave the FDA the authority that it claims, the door would be open to FDA's regulation of all off-label uses, based solely on the manufacturer's knowledge that those uses are common-place. This authority would surely conflict with Congress' will and would eviscerate the long-established foundation of federal food and drug law, which allows, not the FDA, but the manufacturer of the article, through his representations in connection with its sale, [to] determine the use to which the article is to be put.[207]

The decision raised broader questions about FDA's authority in the off-label area, as contemporaneous trade press coverage indicated.[208]

Months after *Western States*, in December 2002, FDA's authority to regulate speech suffered yet another blow. In *Whitaker v. Thompson*, the United States District Court for the District of Columbia held that FDA had failed to follow its own guidelines in determining when a complete ban on commercial speech was reasonable and, consequently, its ban on plaintiffs' vitamin health claims was an unconstitutional restraint on commercial speech.[209] As commentators point out, "[t]his case signifies the courts' gradual departure from the long-standing deference typically granted FDA under the *Chevron* doctrine, and unveils the courts' growing skepticism about FDA's policies and the agency's ability to enforce these policies credibly."[210]

5. *The* Sorrell *Period*

The 2007 through 2011 period involved significant public discussion of new guidance development by FDA to provide a safe harbor for certain publications that included information about off-label uses. This period was punctuated by the seminal Supreme Court decision extending First Amendment protections to "speech in aid of pharmaceutical marketing," and recognizing the need for "heightened judicial scrutiny" of any government restriction that burdens such speech.[211] The decision, in 2011, was a watershed, and precipitated a series of developments reflecting judicial skepticism of government efforts to restrict accurate speech about off-label uses. During this phase, industry litigation efforts were largely successful, with one company—Allergan—using First Amendment arguments proactively to improve its negotiating position in an off-label investigation arising under the False Claims Act.

On November 30, 2007, Representative Henry Waxman sent a letter to FDA Commissioner Andrew von Eschenbach concerning an unpublished draft FDA

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[207] *Id.* at 218 (citations and internal quotation marks omitted).

[208] THE PINK SHEET (Oct. 28, 2002) ("legislative staff are . . . reviewing the decision with an eye towards broader issues it appears to raise about the extent of FDA's authority to demand that prescription drug labeling include warnings related to off-label uses"); THE PINK SHEET, 4 (Oct. 21, 2002) (discussing the "broader implications" of the decision for FDA's power to regulate off-label uses and noting the controversy surrounding FDA's assertion of authority to compel manufacturers to test drugs for uses for which they do not seek approval).

[209] 248 F. Supp. 2d 1, 16–17 (D.D.C. 2002).

[210] Edward M. Basile & Melanie Gross, *The First Amendment and Federal Court Deference to the Food and Drug Administration: The Times They Are A-Changin'*, 59 FOOD & DRUG L.J. 31, 31 (2004) (citation omitted). The lengthy subsequent history of FDA's efforts to regulate claims made by dietary supplement manufacturers is recounted in, for example, *Alliance for Natural Health US v. Sebelius*, 714 F. Supp. 2d 48, 55–56 (D.D.C. 2010).

[211] *See* Sorrell v. IMS Health Inc., 564 U.S. 552, 557 (2011).

guidance dated October 2007.[212] The unpublished draft had reportedly been leaked by an unidentified source within FDA.[213] The draft was intended to "provid[e] [FDA's] current views on the dissemination of medical journal articles and medical or scientific reference publications on unapproved new uses for approved drugs or approved or cleared medical devices marketed in the United States to healthcare professionals and healthcare entities," following the sunset of FDAMA § 401 on September 30, 2006, and the consequent inapplicability of FDA's regulations implementing that section.

The draft recommended that such journal articles: 1) be published by an organization that has an editorial board, uses experts to review and select articles, and fully discloses any conflict of interests or biases of the authors, contributors, or editors; 2) be peer-reviewed; and 3) not be in a publication or supplement funded in whole or in part by the manufacturer of the product discussed in the article.[214] The draft also stated that publications should not be:

- primarily distributed by a drug or device manufacturer; []
- written, edited, excerpted, or published specifically for, or at the request of a drug or device manufacturer; or
- edited or significantly influence by a drug or device manufacturer or any individuals having a financial relationship with the manufacturer.[215]

The draft emphasized that publications should "address adequate and well-controlled clinical investigations" and should not be false or misleading, or pose a significant risk to the public health.[216] The document recommended additional safeguards as to the manner of dissemination, indicating that publications should not be abridged or summarized by the manufacturer and should be accompanied by the approved labeling for the product and distributed separately from any promotional materials.[217]

Representative Waxman expressed concern that the leaked guidance would "carve a large loophole in the law and create a pathway by which . . . manufacturers can promote unapproved (off-label) uses of their products without first obtaining FDA approval by passing out journal articles about the off-label use to physicians."[218] In particular, he noted that journal articles may not provide accurate, validated, and complete information about a drug's safety or efficacy, especially where studies are

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[212] Letter from Henry A. Waxman, Chairman of the Comm. on Oversight and Gov't Reform, to Andrew C. von Eschenbach, M.D., Commissioner, U.S. Food & Drug Admin. (Nov. 30, 2007) [hereinafter Waxman Letter]; U.S. Food & Drug Admin., Draft 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 (Oct. 2007) (unpublished) [hereinafter Leaked Guidance].

[213] *Off-Label Use*, THE PINK SHEET (Dec 14, 2007).

[214] Leaked Guidance, *supra* note 212, at 4–5.

[215] *Id.* at 5.

[216] *Id.*

[217] *Id.* at 5–6.

[218] Waxman Letter, *supra* note 212, at 1.

industry-sponsored,[219] and that allowing off-label promotion would remove the incentive for drug companies to seek FDA approval for such uses.[220] Representative Waxman further requested that FDA send his committee detailed information concerning the basis for the guidance.[221]

On January 22, 2008, Representative Waxman wrote to Commissioner von Eschenbach, noting that FDA had released only a single memorandum from an April 2007 meeting with FDA in which industry had asked the agency to allow the practice of disseminating peer-reviewed journal articles addressing off-label uses. FDA had, Waxman asserted, refused to provide other requested materials on the ground that they contain deliberative "pre-decisional" information.[222]

In February 2008, FDA released a draft guidance document for public comment that was substantively identical to the leaked guidance and did not directly respond to any of Representative Waxman's concerns.[223] Following the conclusion of the comment period, in January 2009, FDA published the guidance in final form.[224] The 2009 guidance was substantially similar to the 2008 draft guidance but also encouraged manufacturers to seek FDA approval for off-label uses and states that "[a]n approved new drug that is marketed for an unapproved use (whether in labeling or not) is misbranded because the labeling of such drug does not include 'adequate directions for use.'"[225]

On November 30, 2009, in *United States v. Caronia*, the United States District Court for the Eastern District of New York sentenced a pharmaceutical sales representative following his conviction for conspiracy to introduce a misbranded drug into interstate commerce drug in violation of the FDCA.[226] The misbranding charge was based on defendant's promotion of the drug Xyrem (sodium oxybate) for an off-label use, which the government charged caused the drug's labeling to lack "adequate directions for use."[227] The district court had earlier denied the defendant's motion to

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[219] *See, e.g.*, *id.* at 8–11. Representative Waxman cites six such journal articles in an addendum to his letter.

[220] *Id.* at 3 (citation omitted).

[221] *Id.* at 6–7.

[222] Letter from Henry A. Waxman, Chairman of the Comm. on Oversight and Gov't Reform, to Andrew C. von Eschenbach, M.D., Commissioner, U.S. Food & Drug Admin. (Jan. 22, 2008) (citing Letter from Stephen R. Mason, Acting Assistant Commissioner for Legislation to Henry A. Waxman, Chairman of the Comm. on Oversight and Gov't Reform (Dec. 21, 2007)).

[223] U.S. FOOD & DRUG ADMIN., GOOD REPRINT PRACTICES FOR THE DISTRIBUTION OF MEDICAL JOURNAL ARTICLES AND MEDICAL OR SCIENTIFIC REFERENCE PUBLICATIONS ON UNAPPROVED NEW USES OF APPROVED DRUGS AND APPROVED OR CLEARED MEDICAL DEVICES—DRAFT GUIDANCE (Feb. 2008).

[224] *See* U.S. FOOD & DRUG ADMIN., *supra* note 51.

[225] *Id.* at 2–3 (citations omitted). The published guidance similarly clarifies that if a manufacturer engages in conduct that unlawfully promotes an unapproved use, even if the manufacturer is also engaging in conduct in accordance with the guidance, such conduct may result in enforcement action. *Id.* at 6.

[226] Judgment as to Alfred Caronia, United States v. Caronia, No. 1:06-cr-0229-ENV (E.D.N.Y. 2009) (ECF No. 126); *see* Jury Verdict as to Alfred Caronia, United States v. Caronia, No. 1:06-cr-0229-ENV (E.D.N.Y. 2008) (ECF No. 103).

[227] Superseding Indictment as to Peter Gleason and Alfred Caronia at 13, United States v. Caronia, No. 1:06-cr-0229-ENV (E.D.N.Y. 2007) (ECF No. 28) (charging defendant with the Introduction of a Misbranded Drug into Interstate Commerce under 21 U.S.C. § 352(f)(1)).

dismiss the charges on the basis that the misbranding provisions of the FDCA violated his First Amendment right to free speech.[228]

In late 2010, Allergan settled a criminal and civil case brought by the Department of Justice (DOJ) following an investigation into its promotion of off-label uses of its drug Botox for therapeutic treatment of headache, pain, spasticity, and juvenile cerebral palsy.[229] As part of this settlement, the company also agreed to drop a lawsuit against FDA seeking a declaratory judgment that, among other things, Section 502(a) of the FDCA and various FDA regulations were unconstitutional as applied to Allergan's planned truthful, non-misleading speech concerning off-label uses.[230] Specifically, Allergan had sought a ruling that speech to healthcare professionals regarding the risk of potential distant spread of toxin effect, particularly when Botox is used off-label in treating children for spasticity—which appeared in a boxed warning and was the subject of an FDA-required risk evaluation and mitigation strategy (REMS) for all botulinum toxin manufacturers.[231]

During that litigation, Robert Temple, Deputy Director for Clinical Science and Acting Director of the Office of Drug Evaluation I in the Office of New Drugs at CDER, asserted that:

> FDA has never considered its concerns about off-label promotion as a basis for preventing sponsors from providing appropriate warnings about the adverse consequences of an off-label use. The warnings should not, of course, represent a 'back door' promotion; that is, they should not explicitly or implicitly promote the efficacy of the unapproved use . . . . A manufacturer could disseminate this information without triggering the prohibitions on distributing a product for an unapproved use and misbranding a product for failure to provide adequate directions for use.[232]

In dropping the lawsuit as part of the settlement, Allergan stated that it was "disappointed that the court was not afforded an opportunity to hear and rule on these important First Amendment issues."[233]

On June 23, 2011, the Supreme Court issued its decision in *Sorrell v. IMS Health Inc.*[234] In *Sorrell*, the Supreme Court struck down a Vermont statute that prohibited the use of physician prescribing records by pharmaceutical companies in their marketing.[235] The statute imposed content and speaker-based burdens, to which the

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[228] United States v. Caronia, 576 F. Supp. 2d 385, 403–04 (E.D.N.Y. 2008), *vacated and remanded by* United States v. Caronia, 703 F.3d 149 (2nd Cir. 2012).

[229] Abigail Rubenstein, *Allergan Settles Botox Off-Label Claims For $600M*, LAW360 (Sept. 1, 2010), https://www.law360.com/articles/190835; *see also* Press Release, U.S. Dep't of Justice, Allergan Agrees to Plead Guilty and Pay $600 Million to Resolve Allegations of Off-Label Promotion of Botox® (Sept. 1, 2010).

[230] Complaint at 38–40, Allergan, Inc. v. United States, No. 1:09-cv-01879-JDB (D.D.C. 2009) (ECF No. 1) [hereinafter Allergan Complaint]; Stipulation of Dismissal, Allergan, Inc. v. United States, No. 1:09-cv-01879-JDB (D.D.C. 2010) (ECF No. 52).

[231] Allergan Complaint, *supra* note 230, at 17–21.

[232] Declaration of Robert Temple, M.D., at 4–6, Allergan, Inc. v. United States, No. 1:09-cv-01879-JDB (D.D.C. Dec. 11, 2009) (ECF No. 18-2).

[233] *See* Rubenstein, *supra* note 229.

[234] *See* Sorrell v. IMS Health Inc., 564 U.S. 552 (2011).

[235] *Id.* at 563–80.

Court applied "heightened judicial scrutiny."[236] The Court concluded that the restrictions violated the First Amendment.[237] Justice Breyer's dissenting opinion referenced FDA's regulation of off-label promotion, which was at issue in *Caronia*. Specifically, the dissent stated that the majority's analysis called into question FDA's ability to "control in detail just what a pharmaceutical firm can, and cannot, tell potential purchasers about its products."[238]

On July 5, 2011, a citizen petition was submitted on behalf of seven members of the Medical Information Working Group (MIWG), requesting that FDA clarify its regulations and policies with respect to certain communications and activities relating to new uses of marketed products.[239] The petition asked FDA to promulgate binding regulations embodying FDA's current policy on responses to unsolicited requests, clearly distinguishing nonpromotional responses to unsolicited requests from product promotion, and clarifying that responses to unsolicited requests are outside the scope of materials that can create an intended use and are not advertising or labeling.[240] The petition also asked FDA to clarify that statements qualify as scientific exchange if they "(1) make clear that a use or product is not FDA-approved or -cleared; (2) make no claims that a use or product has been proven to be safe or effective; and (3) be truthful and non-misleading when measured against available information on the use or product"; and that scientific exchange does not create a new intended use or constitute advertising or labeling.[241] In addition, the petition called on FDA to apply the same scientific exchange principles to drugs and devices.[242] Finally, the petition asked FDA to clarify the extent to which manufacturers could disseminate information regarding investigational products or off-label uses of approved or cleared products, health care economic data concerning unapproved products or uses, and third-party clinical practice guidelines.[243]

In December 2011, FDA published a notice requesting comments on "all aspects of scientific exchange communications and activities related to off-label uses of marketed drugs, biologics, and devices and use of products that are not yet legally marketed."[244] The notice explained that FDA had made "prior statements regarding scientific exchange," and quoted the language from the 1987 preamble.[245] It also posed questions about the meaning of scientific exchange, including:

- "How should FDA define scientific exchange?"

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[236] *Id.* at 570.

[237] *Id.* at 580.

[238] *Id.* at 590 (Breyer, J., dissenting).

[239] Citizen Petition, Docket No. FDA-2011-P-0512 (July 5, 2011) [hereinafter July 2011 Citizen Petition]; *see also* Letter from Jane A. Axelrad, Associate Director for Policy, CDER to MIWG Counsel, Docket No. FDA-2011-P-0512 (Dec. 29, 2011) (interim response to July 2011 Citizen Petition).

[240] *See* July 2011 Citizen Petition, *supra* note 239, at 7.

[241] *Id.* at 9–10.

[242] *Id.* at 9.

[243] *Id.* at 10–12.

[244] Communications and Activities Related to Off-Label Uses of Marketed Products and Use of Products Not Yet Legally Marketed; Request for Information and Comments, 76 Fed. Reg. 81,508, 81,509 (Dec. 28, 2011).

[245] *Id.*

- "What are the distinctions between scientific exchange and promotion?"
- "How should the Agency treat scientific exchange concerning off-label uses of already approved drugs and new uses of legally marketed devices?"[246]

The notice represented an auspicious development from the standpoint of advocates for changes to the regulatory scheme. At the same time, it raised concern and contributed to confusion, because FDA's discussion of scientific exchange and its questions about the scope of that concept suggested that it was considering whether to narrow the scope of manufacturer communications about off-label uses and unapproved products.

6. Developing Case Law

Next was a period of significant developments in the case law, particularly in the First and Fifth Amendment areas. Even as the courts were establishing or reinforcing limitations on FDA's authority to regulate manufacturer speech, either directly or indirectly, prosecutors continued to pursue a range of penalties in cases involving allegations of unlawful off-label promotion.

In June 2012, the Supreme Court issued a First Amendment decision in a different regulatory context—that of the Federal Communications Commission (FCC)—that had important implications for FDA regulation. *FCC v. Fox Television Stations, Inc.* ("*Fox II*") involved an enforcement action against two television networks for broadcasting "obscene, indecent, or profane language."[247] The Supreme Court expressly did not address the First Amendment implications of FCC's policy.[248] Instead, it held that because FCC "failed to give [the networks] fair notice prior to the broadcasts in question that fleeting expletives and momentary nudity could be found actionably indecent . . . the [FCC's] standards as applied to these broadcasts were vague, and the [FCC's] orders must be set aside."[249]

On December 3, 2012, the Second Circuit reversed the defendant's conviction in *United States v. Caronia*.[250] In its initial brief, the United States asserted that "Caronia was not convicted for promoting Xyrem for off-label uses, nor could he have been[,]" since "[p]romoting an approved drug for off-label uses is not itself a prohibited act under the FDCA, nor is it an element of any prohibited act."[251] Instead, the government claimed, off-label promotion "plays an evidentiary role in determining whether a drug is misbranded under 21 U.S.C. § 352(f)(1)[,]" which deems a drug misbranded if its

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[246] *Id.*

[247] 567 U.S. 239, 243 (2012) ("*Fox II*") (citing 18 U.S.C. § 1464).

[248] *Id.* at 258 ("First, because the 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.").

[249] *Id.* at 258.

[250] United States v. Caronia, 703 F.3d 149, 152 (2nd Cir. 2012) ("Caronia argues that he was convicted for his speech—for promoting an FDA-approved drug for off-label use—in violation of his right of free speech under the First Amendment. We agree. Accordingly, we vacate the judgment of conviction and remand the case to the district court.").

[251] Brief and Special Appendix for the United States at 51, United States v. Gleason (Caronia), No. 09-5006-cr, 2010 WL 6351497 (2d Cir. 2010) (citing 21 U.S.C. § 331).

labeling lacks adequate directions for use.[252] And, "[w]hether labeling has adequate directions for a drug's intended use . . . turns in part on the factual question of what the intended uses of the drug actually are[,]" a question on which promotional activities cast light.[253]

In its decision, the Second Circuit rejected the government's claims that it did not prosecute Caronia for off-label promotion.[254] The court of appeals found that prohibiting truthful, non-misleading speech about off-label uses did not withstand First Amendment scrutiny.[255]

On March 5, 2013, Par Pharmaceuticals settled criminal and civil allegations brought by DOJ for Par's promotion of off-label uses for its drug Megace ES.[256] As in Allergan, Par filed a defensive First Amendment lawsuit against FDA, seeking to enjoin it from preventing Par's truthful and non-misleading communications to physicians likely to prescribe Megace ES off-label to treat wasting in non-AIDS patient populations, including geriatric and cancer patients, and as part of the settlement, agreed to dismiss its suit.[257]

7. Progress: 2013–2016

The sequence of disputes discussed above made it inevitable that FDA officials would consider the potential implications of the First Amendment for the agency's approach to off-label information. For more than three years, beginning around 2013, developments in this area appeared relatively constructive to industry. They were characterized by incremental expansion of relevant guidance and FDA's announced decision to grant industry's request for changes to the governing regulatory approach.

On September 3, 2013, the MIWG submitted a second petition to FDA to reiterate the requests originally set forth in its members' still-pending July 2011 petition. The petition asked the agency to provide a clear definition of "scientific exchange." The second petition also asked FDA to take "further steps to reevaluate, and modify as necessary, the Agency's regulations and policies with respect to manufacturer dissemination of new-use information in light of public health considerations, statutory limitations, and recent First and Fifth Amendment case law."[258] FDA issued

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[252] *Id.* (emphasis in original).

[253] *Id.*

[254] *Caronia*, 703 F.3d at 161–62, 164–65.

[255] *Id.* at 165.

[256] Press Release, U.S. Dep't of Justice, Par Pharmaceuticals Pleads Guilty and Agrees to Pay $45 Million to Resolve Civil and Criminal Allegations Related to Off-Label Marketing (Mar. 5, 2013).

[257] Joint Stipulation of Dismissal with Prejudice, Par Pharm., Inc. v. United States, No. 1:11-cv-1820 (D.D.C. 2013) (ECF No. 33); Complaint at 22–26, Par Pharm., Inc. v. United States, No. 1:11-cv-1820 (D.D.C. 2011) (ECF No. 1); *see also* Thomas Sullivan, *Par Pharmaceuticals Settles Off-Label Case, Drops First Amendment Case*, POLICY & MED. (last updated May 6, 2018), https://www.policymed.com/2013/03/par-pharmaceuticals-settles-off-label-case-drops-first-amendment-case.html. In that lawsuit, FDA's Associate Director of Medical Policy within CDER filed a declaration citing four examples of allegedly "significant adverse consequences that have resulted from off-label uses of approved drugs," including one that also appeared in the 1994 *Federal Register* notice. The examples appear to relate solely to alleged harms from off-label *use* of approved drugs, and do not allege any type of off-label promotion. *See* Declaration of Rachel E. Sherman, M.D., at 9–13, Par Pharm., Inc. v. United States, No. 1:11-cv-1820 (D.D.C. 2012) (ECF No. 14-3).

[258] Citizen Petition, Docket No. FDA-2013-P-1079, 2 (Sept. 3, 2013).

an interim response on February 28, 2014, in which it stated, in relevant part, that it continued to evaluate comments on the scientific exchange Federal Register notice.[259]

In February 2014, FDA issued a draft revision of the 2009 Final Guidance "in response to stakeholder questions about its application to scientific and medical reference texts and [clinical practice guidelines (CPGs)]," particularly the July 2011 and September 2013 industry petitions.[260] The 2014 draft guidance separated the recommended practices applicable to the distribution of 1) medical journal articles, 2) scientific or medical reference texts, and 3) CPGs.[261] The 2014 draft guidance also included a revised background description, emphasizing the importance to public health of the FDA premarket review process for approved drugs and medical devices.[262]

The recommendations for the distribution of medical journal articles in the 2014 draft guidance were substantially similar to those included in the 2009 final guidance; however, FDA changed the requirement that an article or text not "pose a significant risk to the public health" to a requirement that such article or text not "[c]ontain information recommending or suggesting use of the product that makes the product dangerous to health when used in the manner suggested."[263] The 2014 draft guidance also required that a distributed reprint not be attached to specific product information (other than the approved product labeling).[264] The recommendations for scientific or medical reference texts and CPGs were specifically tailored to the use and context of those texts; however, the recommendations and disclosure requirements are identical to those required of medical journal articles (and included in prior iterations of the guidance).[265]

FDA responded to both the July 2011 and September 2013 petitions on the merits on June 6, 2014. The agency granted both petitions "to the extent that they seek greater regulatory clarity . . . and, more generally, that FDA engage in a comprehensive review of the regulatory regime governing communications about medical

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[259] *See* Letter from Jane A. Axelrad, Associate Director for Policy, CDER, to MIWG Counsel, Docket No. FDA-2013-P-1079, 2 (Feb. 28, 2014).

[260] U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY—DISTRIBUTING SCIENTIFIC AND MEDICAL PUBLICATIONS ON UNAPPROVED NEW USES—RECOMMENDED PRACTICES 6 (Feb. 2014) [hereinafter FDA, DISTRIBUTING SCIENTIFIC AND MEDICAL PUBLICATIONS]; *see also* 79 Fed. Reg. 11,880 (Mar. 3, 2014).

[261] FDA, DISTRIBUTING SCIENTIFIC AND MEDICAL PUBLICATIONS, *supra* note 260, at 7–17.

[262] *Id.* at 2–7. FDA specifically states that a condition contained in FDAMA § 401 was that "the manufacturer of the product would seek FDA approval for the unapproved new use referenced in the disseminated literature." *Id.* at 5.

[263] *Id.* at 8.

[264] *Id.* at 9.

[265] *See id.* at 10–14. Also in 2014, FDA published additional draft guidance addressing distribution of scientific or medical journal articles that discuss the risks of approved drugs. The agency believed the guidance was necessary "to address the spectrum of data sources that could be appropriate for distribution to provide new risk information[,]" and because "new risk information may contradict or otherwise deviate from the risk information in the approved labeling, which may cause confusion or otherwise contribute to patient harm." FDA explained that the guidance was not, strictly speaking, concerned with the dissemination of information regarding off-label uses, but rather unlabeled risk information about on-label uses. *See* U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY—DISTRIBUTING SCIENTIFIC AND MEDICAL PUBLICATIONS ON RISK INFORMATION FOR APPROVED PRESCRIPTION DRUGS AND BIOLOGICAL PRODUCTS—RECOMMENDED PRACTICES 2 (June 2014).

products."[266] FDA indicated that it planned to issue guidance on "distributing scientific and medical information on unapproved new uses, and manufacturer discussions regarding scientific information more generally, by the end of the calendar year."[267]

On August 7, 2015, Amarin Corporation successfully obtained a preliminary injunction prohibiting FDA from infringing on the company's First Amendment rights with a misbranding action premised on truthful, non-misleading statements about the effectiveness of Amarin's product Vascepa (icosapent ethyl) in reducing "persistently high triglycerides."[268] FDA had indicated in a letter that Vascepa could be considered misbranded based on such statements, on the ground that clinical trials of other manufacturers' drugs had "found that the reduction of triglyceride levels in patients with persistently high triglycerides had had no impact on the risk of cardiovascular events."[269]

In finding that Amarin was likely to succeed on the merits and granting the preliminary injunction, the court stated that "under *Caronia*, the FDA may not bring [a misbranding] action based on truthful promotional speech alone, consistent with the First Amendment."[270] Indeed, the court rejected FDA's arguments that *Caronia* be limited only to specific types of statements regarding off-label use, such as responses to unsolicited requests: "*Caronia's* holding was that the FDCA's misbranding provisions cannot constitutionally criminalize, and therefore do not reach, the act of truthful and non-misleading speech promoting off-label use."[271]

In November 2016, FDA held a two-day public hearing seeking input on manufacturer communications regarding unapproved uses of approved or cleared medical products.[272]

8. Transition to a New Administration

In January 2017, FDA published a "Memorandum" entitled "Public Health Interests and First Amendment Considerations Related to Manufacturer Communications Regarding Unapproved Uses of Approved or Cleared Medical Products."[273] The memorandum was intended to respond to criticism that "FDA had not sufficiently discussed the First Amendment in the notice of the public hearing."[274] In the document, FDA recognized the complexity involved in "[i]ntegrating the many substantial interests" implicated by the dissemination of information about off-label uses "in a way that best promotes public health and comports with recent First Amendment

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[266] Letter from Leslie Kux, Assistant Comm'r for Pol'y, FDA, to MIWG Counsel, Docket Nos. FDA-2011-P-0512 and FDA-2013-P-1079, 2 (June 6, 2014).

[267] *Id.* at 9.

[268] *See* Amarin Pharma, Inc. v. FDA, 119 F. Supp. 3d 196, 237 (S.D.N.Y. 2015). Vascepa had already received FDA approval in patients with "very high triglyceride" levels, but was rejected for a second indication in patients with merely elevated triglyceride levels (i.e., "persistently high" levels of triglyceride).

[269] *Id.* at 211.

[270] *Id.* at 224 (emphasis in original).

[271] *Id.* at 227.

[272] *See* Manufacturer Communications Regarding Unapproved Uses of Approved or Cleared Medical Products; Public Hearing; Request for Comments, 81 Fed. Reg. 60,299, 60,299 (Sept. 1, 2016).

[273] U.S. FOOD & DRUG ADMIN., PUBLIC HEALTH INTERESTS AND FIRST AMENDMENT CONSIDERATIONS RELATED TO MANUFACTURER COMMUNICATIONS REGARDING UNAPPROVED USES OF APPROVED OR CLEARED MEDICAL PRODUCTS (Jan. 2017).

[274] *Id.* at 1.

jurisprudence[.]"[275] The memorandum, FDA explained, was intended to "help advance the dialogue about these issues."[276]

Also in January 2017, FDA issued two draft guidance documents outlining conditions under which it would not consider certain communications as evidence of intended use, or of a manufacturer's failure to provide adequate directions for use, solely because it presents data or information not reflected in the FDA-approved labeling. The first draft guidance outlined three factors the agency would use to determine whether a communication was consistent with the FDA-approved labeling (CFL): 1) how information in communication compares to information about certain conditions of use in FDA-required labeling; 2) whether representations/suggestions in communication increase potential for harm relative to information reflected in FDA-required labeling; and 3) whether directions for use in the FDA-required labeling enable safe and effective use under conditions represented/suggested.[277] A communication was CFL if it met all three factors.[278]

The second draft guidance addressed communications with payors, formulary committees, and similar entities.[279] The draft guidance discussed communications of healthcare economic information (HCEI) to payors regarding approved drugs, and payor communications regarding investigational drugs and devices. In addition to not constituting evidence of intended use and not, on their own, constituting failure to provide adequate directions for use solely because they include information or data not in the FDA-approved labeling, communications made consistent with the recommendations in the document would not be considered promotion of investigational drugs or devices under 21 C.F.R. §§ 312.7(a) or 812.7(a).[280]

In 2017, Congress considered two proposals that would affect FDA's approach on scientific exchange: the Medical Products Communications Act of 2017 as an amendment to the FDA user legislation,[281] and a complementary bill, the Pharmaceutical Information Exchange Act.[282] Under the Medical Products Communications Act of 2017, the intended use of a drug, biological product, or device would not be determined by reference to 1) "actual or constructive knowledge of the manufacturer or sponsor that such drug, biological product, or device will be used in a manner that varies from the use approved for marketing" or 2) "scientific exchange."[283] The Pharmaceutical Information Exchange Act sought to allow manufacturers to provide population health decision makers information similar to "scientific exchange" under certain conditions.[284]

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[275] *Id.* at 3.

[276] *Id.*

[277] FDA, MEDICAL PRODUCT COMMUNICATIONS, *supra* note 24, at 3–5.

[278] *Id.* at 3.

[279] U.S. FOOD & DRUG ADMIN., DRUG AND DEVICE MANUFACTURER COMMUNICATIONS WITH PAYORS, FORMULARY COMMITTEES, AND SIMILAR ENTITIES—QUESTIONS AND ANSWERS (Jan. 2017).

[280] *Id.* at 16.

[281] H.R. 1703, 115th Cong. (2017).

[282] H.R. 2026, 115th Cong. (2017–2018).

[283] H.R. 1703.

[284] H.R. 2026.

On July 12, 2017, the Subcommittee on Health of the House Committee on Energy and Commerce held a hearing on the two measures.[285]

In June 2018, FDA finalized its guidance on communications that are CFL.[286] The final CFL factors were unchanged from the factors in the draft guidance, but the final guidance clarified that FDA "does not intend to rely on" a CFL communication "to establish a new intended use" or "as evidence of a firm's failure to comply with the FD&C Act's requirement that a medical product's labeling bear adequate directions for use[.]"[287] FDA indicated, however, that a CFL communication "may be part of the overall material that is evaluated in assessing the firm's conduct."[288] Also in June 2018, FDA finalized its guidance on communications with payors, formulary committees, and similar entities, along with the CFL guidance discussed above.[289]

9. 2021-Present

On January 13, 2021, two former executives of Acclarent, William Facteau and Patrick Fabian, were sentenced following their 2016 convictions for distributing adulterated and misbranded medical devices.[290] Acclarent had initially received 510(k) clearance for their Stratus devices as a sinus spacer to allow the administration of saline solution.[291] The company later asked FDA to expand the indications for use to include "irrigat[ing] the sinus space for diagnostic and therapeutic procedures," but FDA declined to do so without additional data.[292] Acclarent then conducted a clinical study in which physicians administered the steroid Kenalog-40) into the sinuses using the Stratus device; FDA halted the study in December 2007 after determining that the study raised significant risks.[293] Nonetheless, under the defendants' leadership, Acclarent began marketing the Stratus device for steroid delivery without FDA approval or clearance, even after the company's merger partner Ethicon instructed

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[285] The discussion draft included important changes from the 2017 Proposed Legislation, including, 1) an additional safe harbor for "non-public statements about the drug or device that are not reflected in any claim, promotional statement or material, or circumstances surrounding the distribution of the drug or device that involve interactions with third parties;" and 2) additional requirements to the definition of "scientific exchange" that "the communication is not advertising or otherwise promotional in nature," and "the communication clearly discloses appropriate contextual information about the data presented, including information about . . . (1) the limitations of the data; (2) the scientific and analytical methodologies used; and (3) . . . any contradictory data or information known to the manufacturer or sponsor." Examining Medical Product Manufacturer Communications: Hearing Before the Subcommittee on Health of the Committee of Energy and Commerce House of Representatives, 115th Cong. (2017).

[286] U.S. FOOD & DRUG ADMIN., MEDICAL PRODUCT COMMUNICATIONS THAT ARE CONSISTENT WITH THE FDA-REQUIRED LABELING: QUESTIONS AND ANSWERS—GUIDANCE FOR INDUSTRY (June 2018), https://www.fda.gov/media/133619/download.

[287] *Id.* at 8.

[288] *Id.*

[289] *See generally*, *id.*

[290] Nate Raymond, *Judge Apologizes for Four-Year Delay in Sentencing Former Medical Device Execs at J&J Unit*, REUTERS (Jan. 13, 2021), https://www.reuters.com/article/health-acclarent/judge-apologizes-for-four-year-delay-in-sentencing-former-medical-device-execs-at-jj-unit-idUSL1N2JO2PA; *see also* Press Release, U.S. Dep't of Justice, Former Acclarent, Inc. Executives Convicted of Crimes Related to the Sale of Medical Devices (July 20, 2016); *see also* Jury Verdict as to William Facteau, United States v. Facteau, No. 1:15-cr-10076 (D. Mass. 2016) (ECF No. 432).

[291] Indictment at 7–8, United States v. Facteau, No. 1:15-cr-10076, (D. Mass. 2015) (ECF No. 1).

[292] *Id.* at 8.

[293] *Id.* at 8–9.

Acclarent to stop marketing Stratus for any use and to report to FDA that it was "aware that 'our physician customers predominantly choose' to use the Stratus with a drug rather than saline."[294] The defendants appealed to the First Circuit.

On November 24, 2021, the U.S. Solicitor General filed a brief in the First Circuit appeal of the Facteau/Fabian matter. The brief first rejected the appellants' argument that "intended use" in the FDCA and FDA regulations, either by their text, their judicial interpretation, or FDA's change in interpretation of its regulations or theory of prosecution, were unconstitutionally vague and that their prosecution thus violated due process.[295] In addition, the government emphasized FDA's position that the August 2021 final rule made no change to the standard under which the case was tried.[296]

The government also rejected the defendants' arguments that their prosecution imposed a de facto prohibition on truthful promotional speech, in contradiction of *Caronia*, and that FDA's guidance documents creating safe harbors for certain manufacturer-supported activities that would not be treated as evidence of intent constituted unconstitutional content or viewpoint discrimination.[297] In particular, the government stressed "the settled principle that the use of speech as evidence does not implicate the First Amendment[,]" and reiterated the district court's distinguishing of the present case, in which speech was used as evidence of intended use rather than itself constituting the violation, from *Caronia* and *Amarin*.[298]

Likewise, the government's brief rejected the First Amendment arguments of amici PhRMA and WLF on the ground that the defendants were not prosecuted for or convicted of FDCA violations premised exclusively on truthful, non-misleading speech.[299] As to Due Process, the brief contends that there was never confusion regarding the interpretation of intended use; the August 2 final rule makes clear that the expansive interpretation of intended use was always the law; and the only change effected by the final rule was the removal of the knowledge prong, which was not at issue in the appeal.[300]

With respect to the safe harbors, the brief contends that the defendants never argued that they had acted in reliance on any such policy.[301] Moreover, the district court's instructions had accounted for FDA's guidance on responses to unsolicited requests.[302] The brief also asserted that "decades of precedent" support the government's expansive reading of intended use.[303]

On October 24, 2023, FDA published a new document entitled, Communications From Firms to Health Care Providers Regarding Scientific Information on

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[294] *Id.* at 12–20.

[295] Brief for the United States (Corrected) at 32, 34–48, United States v. Facteau, No. 21-1080 (1st Cir. 2021) (ECF No. 00117817400) ("Facteau US Brief").

[296] *Id.* at 46–47.

[297] *Id.* at 48–62.

[298] *Id.* at 50, 54–58.

[299] *Id.* at 88–91.

[300] *Id.* at 91–93.

[301] *Id.* at 92–93.

[302] *Id.*

[303] *Id.*

Unapproved Uses of Approved/Cleared Medical Products: Questions and Answers.[304] The document is a revised version of a 2014 draft guidance document, which in turn revised the 2009 final guidance document addressing reprints and textbooks, discussed above. In issuing the revised draft on October 24, FDA appears to have departed from its established approach to these types of scientific and medical communications. The document encompasses additional categories of communications, and purports to adopt new standards for the content and format of materials disseminated under the guidance. It also appears to reflect FDA's determination that the rationale for manufacturer communications to health care practitioners is limited to the role that such individuals play in providing clinical care, and that such rationale should not extend to the interest that practitioners may have in receiving scientific information that is accurate and substantiated and therefore valuable in its own right. In other words, FDA appears to be indicating that the only legitimate interest that this type of communication could serve is the need for clinicians to inform themselves to facilitate patient-specific decisions. That vision of medical communications raises important First Amendment issues and will surely be the subject of stakeholder comments submitted to FDA in response to the revised draft guidance document.

III. FDA'S INTENDED USE RULEMAKING (2015–2021)

The rulemaking began with FDA's publication of a proposed rule in the Federal Register on September 25, 2015.[305] In connection with rulemaking relating to FDA's implementation of the Family Smoking Prevention and Tobacco Control Act of 2009, the agency said it was "taking the opportunity to propose corresponding changes to existing regulations at 21 CFR § 201.128 and § 801.4, and to conform them to how the Agency currently applies these regulations to drugs and devices generally."[306] In particular, FDA proposed to remove language that industry had long regarded as authorizing the agency to find a new intended use (and accordingly a violation of the FDCA off-label promotion prohibitions) for a marketed drug or device based solely on the manufacturer's knowledge that its product was being put to that use.

As FDA explained the proposed rule, it was established agency practice not to regard a manufacturer's knowledge of off-label use, without more, as establishing a new intended use. At the same time, however, the agency's authority to rely on a range of different evidentiary types remained broad. In addition to the manufacturer's promotional claims, FDA could "consider . . . a variety of direct and circumstantial evidence," including "any circumstances surrounding the distribution of the product

[304] Communications From Firms to Health Care Providers Regarding Scientific Information on Unapproved Uses of Approved/Cleared Medical Products: Questions and Answers; Revised Draft Guidance for Industry; Availability; Agency Information Collection Activities; Proposed Collection; Comment Request, 88 Fed. Reg. 73,031 (Oct. 24, 2023).

[305] Clarification of When Products Made or Derived From Tobacco Are Regulated as Drugs, Devices, or Combination Products; Amendments to Regulations Regarding "Intended Uses," 80 Fed. Reg. 57,756 (proposed Sept. 25, 2015). As its title indicates, the proposed rule comprised two distinct (but related) parts, only the second of which is relevant here.

[306] *Id.* at 57,756. The tobacco-specific changes were, the FDA explained, intended to "increase clarity regarding the types of claims and other evidence that make a product made or derived from tobacco subject to regulation as a drug, device or combination product, helping consumers distinguish products made or derived from tobacco that are intended for medical use from products marketed for other uses." *Id.*

or the context in which it is sold[.]"[307] The proposed rule thus would have made clear that "the Agency would not regard a firm as intending an unapproved new use for an approved or cleared medical product based solely on the firm's knowledge that such product was being prescribed or used by doctors for such use," though it could find a new intended use based on any other "relevant" source.[308]

Industry comments submitted in response to the proposed rule generally supported FDA's approach. The MIWG, which had earlier petitioned FDA to amend the intended use regulations, commended the agency but also advanced two further requests.[309] First, the comments asked that the finalized version of the rule make clear that only promotional claims could be considered by FDA in the agency's intended use analyses.[310] Second, the comments noted that the ongoing prosecution of two Acclarent executives had treated knowledge of off-label uses as intended use evidence, and therefore asked FDA to work with federal prosecutors to assure that they were proceeding in accordance with what the proposed rule's preamble had described as established FDA policy.[311]

The final rule published on January 9, 2017, included a final sentence that had not appeared in the proposed rule. It provided that, "if the totality of the evidence establishes that a manufacturer objectively intends that" a drug or medical device "is to be used for conditions, purposes, or uses other than ones for which it has been approved, cleared, granted marketing authorizations, or is exempt from premarket notification requirements (if any), he is required . . . to provide for such drug adequate labeling that accords with such other intended uses."[312] The final rule thus departed significantly from the text of the proposed rule, asserting that FDA could find a new intended use according to a "totality" standard.

This new language was regarded as capacious and lacking in clarity, prompting industry to file a petition requesting that FDA stay the effective date of the final rule and reconsider this aspect of the amendment. Of particular concern to industry was the potential for a broad, new intended use definition to permit the government to find a new intended use based on manufacturer statements that were within the scope of a safe harbor. In filing the petition for stay and reconsideration, the MIWG was joined by the major trade associations, and FDA ultimately granted the stay and published a new proposed rule on September 23, 2020.[313]

The second proposed rule sought to resolve the definitional dispute by removing the "totality" provision entirely, and by adding a new proviso:

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[307] *Id.* at 57,757 (citations omitted).

[308] *Id.* (citing Defendant's Memorandum of Points and Authorities in Support of Motion to Dismiss or Summary Judgment, Allergan Inc. v. United States, 1:09-cv-01879-JDB (D.D.C. 2010) (ECF No. 27)).

[309] Letter from the Medical Information Working Group (MIWG) to Division of Dockets Management, U.S. Food & Drug Admin., Docket No. FDA-2015-N-2002 (Nov. 24, 2015).

[310] *Id.* at 2.

[311] *Id.* at 3. The main trade association for medical device manufacturers, AdvaMed, also submitted comments supporting the removal of the knowledge prong from the definition of intended use. *See* Letter from Khatereh Calleja, JD, Senior Vice President, Technology & Regulatory Affairs, AdvaMed to Division of Dockets Management, U.S. Food & Drug Admin., Docket No. FDA02015-N-2002 (Dec. 18, 2015).

[312] *See* Clarification of When Products Made or Derived From Tobacco Are Regulated as Drugs, Devices, or Combination Products; Amendments to Regulations Regarding "Intended Uses," 82 Fed. Reg. 2,193, 2,206 (Jan. 9, 2017) (withdrawn final rule).

[313] *See* Regulations Regarding "Intended Uses," 85 Fed. Reg. 59,718 (Sept. 23, 2020) (proposed rule).

> ("provided, however, that a firm would not be regarded as intending an unapproved new use for an [approved or cleared medical product] based solely on that firm's knowledge that such [product] was being prescribed or used by health care providers for such use") to clarify that a firm's knowledge that health care providers are prescribing or using its approved or cleared medical product for an unapproved use would not, by itself, automatically trigger obligations for the firm to provide labeling for that unapproved use.[314]

At the same time, FDA "proposed amending the text of §§ 201.128 and 801.4 to provide additional clarification regarding the types of evidence that are relevant to determining a product's intended uses."[315] "Additional clarification," FDA noted, "is provided in the preamble."[316]

The preamble accompanying the new proposed rule exacerbated industry concerns about the breadth of FDA's asserted authority to find a new intended use. In particular, FDA explained that it had intended to convey, in both the 2015 proposed rule and in the 2017 final rule, that "any relevant source of evidence, including a variety of direct and circumstantial evidence," could be used to evaluate the intended use of a product.[317] The 2020 proposed rule preamble asserted, as well, that the "totality" standard included in the 2017 final rule was intended only to capture these concepts. In response to comments indicating that the intended use definition was properly limited to promotional claims, FDA said that "[c]onsidering evidence other than express claims often ensures that FDA is able to pursue firms that attempt to evade FDA medical product regulation by avoiding making express claims about their products."[318] The preamble further defended the broad interpretation as no real threat to manufacturers' safe-harbored communications. For one thing, FDA asserted, the rule merely "describes evidence that may be relevant to establishing intended use" and "does not dictate that certain evidence will be determinative of intended use in an individual case."[319] For another, FDA was not changing any of its "policies and practices . . . regarding the types of firm communications that ordinarily would not, on their own, establish the firm's intent that an approved or cleared medical product be used for an unapproved use."[320] The preamble thus sought to reassure commenters that manufacturer communications "consistent with the recommended practices described in FDA guidance" would not, in and of themselves, "be evidence of a new intended use."[321]

The fine distinctions that FDA sought to establish in the preamble illustrate one of the constitutional problems with the rulemaking. In essence, the agency appears to have set up a three-category taxonomy for various sources of evidence under the intended use regulations: 1) evidence that FDA regarded as determinative of or

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[314] *Id.* at 59,720.

[315] *Id.*

[316] *Id.*

[317] *Id.* at 59,721 (internal quotation marks omitted).

[318] *Id.* at 59,723.

[319] *Id.*

[320] *Id.*

[321] *Id.*

establishing intended use; 2) evidence that FDA would treat as relevant to an intended use determination but which would not be enough, without more, to comprise a new intended use; and 3) evidence that would be deemed simply not relevant to intended use and therefore could reasonably be regarded as genuinely safe harbored. In the 2020 proposed rule preamble, FDA assigned safe harbored communications to the second category, leaving manufacturers uncertain as to whether those communications would be cited in an investigation or enforcement action even when made in accordance with the recommendations provided in FDA guidance. Lacking clear, *a priori* standards for accurate speech regarding off-label uses, the regulatory scheme as described in the preamble does not comport with applicable constitutional limitations, as industry comments pointed out.

In the final rule published on August 2, 2021, FDA finalized amendments to the intended use definitions that tracked the broad, flexible approach that encompassed "any relevant source of evidence," including "a variety of direct and circumstantial evidence."[322] The final rule also made clear that a new intended use could be found based only on the "design or composition" of the product or on "the circumstances surrounding the distribution" of the product.[323] Instead of a claims-based standard under which non-claims evidence could be cited only on an exceptional basis, the newly finalized definition allowed FDA to find a new intended use, at its option, with reference to any of these three categories of evidence. In addition, as discussed further below, FDA asserted that it would be permissible for the agency to rely on either or both of the manufacturer's knowledge of off-label use and manufacturer communications about off-label uses as part of an agency determination that a new intended use has been created.[324]

Under the amended regulations, FDA asserts that many activities long regarded as safe harbored, such as responses to unsolicited requests, are no longer categorically protected. The final rule preamble identifies five "safe harbor" guidance documents describing circumstances in which manufacturers are permitted to disseminate information that is not directly taken from product labeling, including information about "off-label" uses: 1) communications consistent with FDA-approved labeling; 2) payor communications; 3) industry-supported scientific and educational activities; 4) responses to unsolicited requests (draft); and 5) distribution of scientific and medical publications (scientific or medical journal articles, scientific or medical reference texts, and clinical practice guidelines) (draft).[325] Although the preamble asserts that nothing in the final rule reflects a change in these policies, it also states that FDA can point to safe-harbored communications as evidence of a new intended use.[326] The preamble asserts that, under FDA's approach to intended use, these types of firm communications "ordinarily would not, on their own," establish a firm's intent that a

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[322] Regulations Regarding "Intended Uses," 86 Fed. Reg. 41,388 (Aug. 2, 2021) (codified at 21 C.F.R. §§ 201.128, 801.4).

[323] *Id.* at 41,401.

[324] *Id.* at 41,387–88.

[325] *Id.* at 41,396 (citing Regulations Regarding "Intended Uses," 85 Fed. Reg. 59,718, 59,725 (Sept. 23, 2020) (proposed rule)).

[326] Regulations Regarding "Intended Uses," 86 Fed. Reg. at 41,393.

lawfully marketed medical product be used for an unapproved use.[327] But those communications would be relevant to the manufacturer's intent that a medical product be used off-label, according to FDA.[328] The preamble thus calls into question whether ostensibly safe-harbored communications are, in fact, immunized from FDA consideration in evaluating whether a new intended use has been established for a marketed drug or medical device.

Additional questions arise from the status of certain FDA guidance documents that establish safe harbors for certain types of manufacturer communications. With respect to responses to unsolicited requests and the dissemination of scientific and medical publications, the relevant guidance documents are in draft and do not reflect current FDA policy. Indeed, FDA acknowledges the different status of communications undertaken in reliance on a draft safe harbor guidance, noting that a guidance reflects current agency policy only after it has been finalized.[329] Although it is common for manufacturers to rely on draft guidances published by FDA, in the area of communications, doing so would require a manufacturer to accept the risk that the communication would be used against it as intended use evidence, even if the communication were executed consistently with the recommendations in the applicable draft.

In the final rule preamble, FDA does not rule out relying on knowledge as evidence of a new intended use. Under the codified text of the amended regulations, a firm would not be regarded as intending an unapproved new use "based solely on that firm's knowledge that such drug was being prescribed or used by health care providers for such use."[330] According to FDA, the word "solely" means that FDA does not intend to consider a firm's knowledge of off-label use, by itself, as sufficient to establish intended use.[331] That means a firm's knowledge of off-label use could be cited by FDA to help establish a new intended use. Thus, "relevant sources" of evidence "may include" a firm's knowledge that a healthcare provider has used or prescribed the firm's medical product for an unapproved use, according to FDA.[332]

The preamble also states that "a firm's knowledge of off-label use plus safe-harbored communication would not, without more, be determinative of a new intended use," but that statement likewise indicates that both knowledge and safe-harbored communications could be cited to conclude that a new intended use has been created, if there were additional "relevant" evidence such as an "expression" by or on behalf of the manufacturer, or the design of composition of the product.[333] The preamble

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[327] *Id.*; *see also id.* at 41,396 (The final rule "does not reflect a change in FDA's policies and practices regarding the types of firm communications that ordinarily would not, on their own, establish a new intended use.").

[328] *Id.* at 41,388.

[329] FDA has not directly addressed whether activities undertaken in accordance with a draft guidance will be accorded the same (albeit limited) protection as those undertaken in accordance with a final guidance. *See* Regulations Regarding "Intended Uses," 85 Fed. Reg. at 59,723 n.7 (describing even the draft guidances as "recognized").

[330] Regulations Regarding "Intended Uses," 86 Fed. Reg. at 41,401.

[331] *Id.* at 41,397.

[332] *Id.*; *see also id.* ("[A]lthough the healthcare provider's use is not under the firm's control, what may be relevant to intended use is the firm's knowledge that the article is being used by the healthcare provider.").

[333] *Id.* at 41,396 (citing Regulations Regarding "Intended Uses," 85 Fed. Reg. at 59,725).

asserts that the final rule is intended to provide "clarity and direction" regarding the types of evidence relevant to determining a product's intended uses.[334] In reality, the final rule purports to transform the regulatory definition of intended use from an objective standard based primarily on claims into a much broader and potentially standardless concept based on an unexplained notion of "relevance." According to the codified text, "intended use" means "objective intent," which "may be shown" by any of several sources of evidence, at FDA's discretion.[335] Indeed, FDA asserts that "determining a product's intended use is a fact-specific inquiry," in which "FDA may consider all relevant sources of evidence," which are not limited to the sources identified in the codified text.[336] Beyond "relevance," the preamble sheds no light on a governing principle applicable to intended use determinations. The preamble, instead, states that in fulfilling its mission to protect the public health, FDA will evaluate the "individual and unique circumstances of each case" in determining a product's intended use.[337] The preamble notes, further, that in some cases, "a single piece of evidence may be dispositive," while in others, "several elements combined may establish a product's intended use."[338]

The final rule chills accurate manufacturer communications regarding off-label uses and therefore raises significant constitutional concerns. As explained above, the preamble accompanying the final rule makes clear that communications undertaken in reliance on even those safe-harbor policies that FDA characterizes as firmly established are not, in fact, safe harbored. Instead, they can be used by FDA as evidence of intended use, subject only to the limitation that FDA would not use the communications as the exclusive basis on which to find a new intended use. The final also reduces the level of clarity in the regulatory and enforcement framework because it recasts the intended use definition using a flexible standard constrained only by FDA's own views as to what is "relevant" from within the undefined category of "direct and circumstantial" evidence.

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[334] *Id.* at 41,384.

[335] *Id.* at 41,401.

[336] *Id.* at 41,397; *see also* Clarification of When Products Made or Derived From Tobacco Are Regulated as Drugs, Devices, or Combination Products; Amendments to Regulations Regarding "Intended Uses," 82 Fed. Reg. 2,193, 2,208 (Jan. 9, 2017) (withdrawn final rule) (listing additional "relevant" sources of evidence, such as "consumer intent" and "evidence of claims that were never communicated to the public").

[337] Regulations Regarding "Intended Uses," 86 Fed. Reg. at 41,387 n.3; *see also* Regulations Regarding "Intended Uses," 85 Fed. Reg. at 59,724 (same).

[338] Regulations Regarding "Intended Uses," 86 Fed. Reg. at 41,387 n.3; *see also id.* at 41,397 ("Each scenario described in the preamble is fact-specific, and, under other circumstances or in other contexts, similar material may be evaluated differently."); Regulations Regarding "Intended Uses," 85 Fed. Reg. at 59,726 ("Each scenario is fact-specific, and, under other circumstances or in other contexts, similar material may be evaluated differently.").

IV. CHANGING THE FDA REGULATORY SCHEME TO RESPECT FIRST AND FIFTH AMENDMENT LIMITATIONS: THE PATH FORWARD

The Free Speech Clause of the First Amendment prohibits the government from restricting accurate speech regarding lawful activity,[339] and the Fifth Amendment compels the government to provide regulated parties with "fair notice of conduct that is forbidden or required."[340] Ambiguous regulatory standards present even greater constitutional concerns when a lack of clarity could chill protected speech.[341] Vague and overbroad regulation is "particularly treacherous" because the threat of sanctions would deter a party "seek[ing] to exercise protected First Amendment rights."[342] An interpretation of the FDCA that "legalizes the outcome—off-label use—but prohibits the free flow of information that would inform that outcome, . . . does not directly advance [the government's] interest either in reducing patient exposure to off-label drugs or in preserving the efficacy of the FDA drug approval process."[343]

Indeed, the lack of clarity reflected in the final rule, and the chill it imposes on protected manufacturer speech, threaten the established federal policy of balancing enforcement of the FDCA against the need for manufacturers to have clearly defined avenues to use in sharing accurate information regarding off-label uses. As the Second Circuit recognized in 2012, "in the fields of medicine and public health, 'where information can save lives,' it only furthers the public interest to ensure that decisions about the use of prescription drugs, including off-label usage, are intelligent and well informed."[344]

The FDA rulemaking establishing a new and broad interpretation of intended use under the FDCA has upended—in one fell swoop—decades of development of safe-harbor policies ostensibly intended to assure adequate channels of communication by manufacturers about off-label uses of drugs and medical devices. The objective of these policies ultimately is to facilitate appropriate patient care, as 1) manufacturers uniquely have access to a significant amount of important information about off-label uses, and 2) off-label uses are a constituent part of medical and surgical practice and may even represent the standard of care. The final rule was published against the

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[339] *E.g.*, United States v. Caronia, 703 F.3d 149, 160 (2nd Cir. 2012) (invoking the canon of constitutional avoidance to construe the FDCA as not criminalizing the promotion of a drug's off-label use).

[340] FCC v. Fox Television Stations, Inc., 567 U.S. 239, 253 (2012) ("*Fox II*").

[341] *Id.* at 254–55 (citing Reno v. Am. Civil Liberties Un., 521 U.S. 844, 870–71 (1997) ("The vagueness of [a content-based regulation of speech] raises special First Amendment concerns because of its obvious chilling effect.").

[342] Buckley v. Valeo, 424 U.S. 1, 76–77 (1976); *see also* Keyishian v. Bd. of Regents of the U. of N.Y., 385 U.S. 589, 604 (1967) (noting that "'standards of permissible statutory vagueness are strict in the area of free expression . . . [b]ecause First Amendment freedoms need breathing space to survive, government may regulate in the area only with narrow specificity'") (quoting NAACP v. Button, 371 U.S. 415, 438 (1963)).

[343] *Caronia*, 703 F.3d at 167.

[344] *Id.* (quoting Sorrell v. IMS Health Inc., 564 U.S. 552, 566 (2011)); *see also* Dissemination of Information on Unapproved/New Uses for Marketed Drugs, Biologics, and Devices, 63 Fed. Reg. 64,556, 64,579 (Nov. 20, 1998) (codified at 21 C.F.R. § 99.1(b)) (recognizing the "public health gains associated with the earlier dissemination of objective, balanced, and accurate information on important unapproved uses of approved products").

backdrop of developments in constitutional law, the result of which is a stark conflict between First and Fifth Amendment limitations on government regulation of speech, and a broad interpretation of FDA's speech regulatory authority that would chill a significant amount of accurate manufacturer communication regarding lawful activity.

Alternatives to the current FDA regulatory approach for off-label communications have been advanced by academics, industry, and FDA itself. The major extant proposals could be organized into four broad categories: 1) allowing unfettered off-label promotion as long as it is truthful and non-misleading, 2) allowing limited off-label promotion with some FDA oversight at the time the promotion occurs, 3) providing for the more rapid incorporation of information about off-label uses into approved labeling, and 4) reforming the existing FDA "safe harbor" policies allowing manufacturers to disseminate information about off-label uses in carefully defined sets of circumstances.[345]

The alternatives have their own downsides. Under one possible approach, FDA could simply address problematic off-label use by regulating it directly, rather than indirectly through manufacturer speech. Indeed, that is precisely the technique that FDA briefly attempted decades ago, only to abandon it in the face of forceful opposition from physicians.[346] Other ideas have drawbacks of their own. Any approach

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[345] Some other novel proposals that do not fit neatly within this taxonomy include more procedurally oriented ideas, such as establishing a new advisory opinion mechanism, akin to what is available under the federal Anti-Kickback Statute, and relying on a third party, analogous to the Pharmaceutical Advertising Advisory Board (PAAB) and potentially to include some kind of participation from FDA, to review proposed manufacturer communications about off-label uses to determine whether they are appropriate for broader distribution. *See* Letter from Medical Information Working Group to U.S. Food & Drug Admin., Div. of Dockets Management, Amended Comments of the Medical Information Working Group for the Food and Drug Administration Transparency Task Force, Docket No. FDA-2009-N-0247 (Apr. 15, 2010); DUKE-MARGOLIS CTR. FOR HEALTH POL'Y, POLICY OPTIONS FOR OFF-LABEL COMMUNICATION: SUPPORTING BETTER INFORMATION, BETTER EVIDENCE, AND BETTER CARE 8–9 (Feb. 2016). The report identifies five principles to guide FDA's off-label communications policy: 1) sufficient clarity to protect the public health and to avoid chilling dissemination of accurate, reliable, and balanced information; 2) supporting FDA's role in reviewing efficacy claims by clarifying the scope of promotional claims for an approved product that trigger prior FDA review; 3) reducing inconsistencies across FDA's enforcement actions; 4) reforming policy to reduce the need for continued cycles of litigation; and 5) encouraging the development and submission to FDA of additional data on off-label uses. The report recommended that FDA take administrative actions to clarify and make consistent off-label communication policy at the agency and with other relevant enforcement agencies, including the Department of Health and Human Services (HHS) Office of the Inspector General (OIG), the Federal Trade Commission (FTC), and DOJ. Its recommendations include clarifying concepts such as "labeling," "scientific exchange," and "intended use" and creating a centralized, clearly structured resource for FDA's policy, determining how information, particularly information that would not meet standards for labeling, can be incorporated into efficacy claims and product labeling, and FDA engagement with an external entity to review sponsor evidence and associated communications about off-label use and approve them for broader distribution.

[346] Coleen Klasmeier & Martin H. Redish, *Off-Label Prescription Advertising, the FDA and the First Amendment: A Study in the Values of Commercial Speech Protection*, 37 AM. J.L. & MED. 315, 323 (2011); *see also* Bierne, *supra* note 67, at 1553–55. A further factor complicating efforts to render the existing regulatory and enforcement approach constitutional arises out of societal expectations that the government will not interfere with the patient's supposed "right to try." There is evidence that patients (and other stakeholders, including many health care practitioners) would resist any policy that they perceive as involving interference with the individual's asserted entitlement to use any method of treatment they believe could be effective in addressing a health condition, regardless of its regulatory status or the availability of efficacy data from randomized, controlled clinical investigations or other similar sources. *See, e.g.*, Justin Jouvenal & Andrew Jeong, *Court Orders Virginia Hospital to Allow Outside Physician to Provide Ivermectin to COVID-19 Patient*, WASH. POST (Dec. 16, 2021), https://www.washingtonpost.com/health/2021/12/16/virginia-ivermectin-covid-fauquier-hospital/. ("Fauquier County Circuit Court Judge James P. Fisher did not rule on the efficacy of ivermectin, but said in his opinion that the Davies family can pursue

that would provide for continued direct regulation of scientifically supported, properly contextualized communications by manufacturers about the off-label uses of their products would raise the same kinds of constitutional issues discussed above. Ultimately, the option most likely to account for all of the relevant considerations involves providing greater clarity and certainty in the regulatory scheme by clarifying and codifying the safe harbors, so that manufacturers have both adequate channels through which to provide accurate information about their products, and the clear, a priori standards commanded by the Fifth Amendment as applied by the Supreme Court in the *Fox II* decision.

FDA should address the adverse consequences of the final rule and the preamble by clarifying the types of manufacturer communications about off-label uses that are safe harbored, meaning they will not be regulated directly as labeling or advertising under the FDCA and also will not be treated as evidence of the manufacturer's intent that its product be used off-label. FDA should move as quickly as is practicable to set forth its policies on manufacturer communications about off-label uses in binding regulations, promulgated through notice-and-comment rulemaking, to facilitate the dissemination of accurate, scientifically substantiated information about new uses of approved products. Such standards are necessary to assure that FDA's regulatory approach accomplishes its long-standing policy objective of balancing the need for FDCA enforcement with the need to provide appropriate information to support the proper use of medical products in patient care. They are also necessary to assure that manufacturers have appropriate latitude to provide accurate information about off-label uses as required by the First Amendment.

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the treatment because of state and federal 'Right to Try' laws that allow terminally ill patients to try unproven cures when all other options are exhausted, among other legal reasoning.").