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Embracing 21st Century Information  
Sharing: Defining a New Paradigm  
for the Food and Drug Administration's  
Regulation of Biopharmaceutical  
Company Communications  
with Healthcare Professionals

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# **Embracing 21st Century Information Sharing: Defining a New Paradigm for the Food and Drug Administration’s Regulation of Biopharmaceutical Company Communications with Healthcare Professionals**

**BY JAMES M. SPEARS, JEFFREY K. FRANCER,  
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## **INTRODUCTION**

The U.S. Food and Drug Administration (FDA) plays a unique role in protecting the public health and minimizing the risk of the distribution of unsafe or ineffective medicines in the United States. Perhaps equally as important for public health, however, is the need for healthcare professionals to be well informed about the benefits and risks of the medicines they prescribe. In this way, information sharing is critical to healthcare delivery, including information about approved uses of medical treatments as well as medically accepted alternative uses of FDA-approved medicines. Because medical technologies rapidly evolve, a physician’s ability to prescribe treatments for approved as well as alternative, but medically appropriate, uses can enhance the delivery of healthcare to patients.<sup>1</sup> It is not feasible for the drug approval process for supplemental uses of approved medicines to keep pace with all medical advancements. As one FDA leader has noted, “[i]t is inevitable that there will be preliminary support for off label uses before definitive information becomes available.”<sup>2</sup>

FDA’s current interpretation of laws and regulations governing healthcare communications prohibits biopharmaceutical companies from sharing certain accurate, data-driven information about FDA-approved uses and medically accepted<sup>3</sup> alternative

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<sup>1</sup> See Joseph W. Cranston et al., *Report of the Council on Scientific Affairs: Unlabeled Indications of Food and Drug Administration-Approved Drugs*, 32 DRUG INFO. J. 1049 (1998).

<sup>2</sup> *Testimony on Supplemental Indications for Approved Prescription Drugs Before the H. Comm on Government Reform & Oversight, Subcomm. on Human Resources & Intergovernmental Relations*, 104th Cong. 2 (1996) [hereinafter *Testimony*] (statement of Michael Friedman, then-Deputy Commissioner for Operations, FDA) (“Off label uses, particularly for oncology, rare diseases, and pediatrics, can be of great value. Some off label uses have been of great historical importance. Use of beta blockers in hypertension and angina preceded labeling for these uses by many years. It is inevitable that there will be preliminary support for off label uses before definitive information becomes available. Physicians confronted with patient needs, may choose to act on such data, especially where there are no good alternatives.”).

<sup>3</sup> In this article, the term “medically accepted alternative use” means a use that is outside of FDA-approved labeling that is nevertheless listed in specific compendia, supported by clinical practice guidelines, or reimbursed by the federal government or a majority of commercial health insurers. We also note that information or data that is deemed “off-label” by FDA may include (1) information that is consistent with the approved use but that has not been demonstrated by FDA’s evidentiary standards for approval (typically two double-blind placebo controlled studies), (2) information pertaining to medically accepted alternative

uses of FDA-approved drugs with healthcare professionals. Often, these uses are the standard of care for good medical practice and are, accordingly, reimbursed under the federal healthcare programs. Although FDA has acknowledged the importance of prescribing approved medicines for unapproved uses and noted that manufacturers often have unique insight into these practices, FDA has failed to describe adequately how manufacturers can share truthful and non-misleading information about such uses. This failure could impede medical innovation, negatively impact patient care, and increase healthcare costs. Thus, to improve public health, FDA should reform its current approach and provide manufacturers with a clear safe harbor on how to share data and information on both approved uses and medically accepted alternative uses of FDA-approved drugs with healthcare professionals. This Article describes key principles for a new regulatory paradigm.

In Section I, we explore various sources that educate and inform healthcare professionals about the medicines they prescribe, discuss the patient need for prescribing FDA-approved medicines for both approved and medically accepted alternative uses for some patients and conditions, and explain how the current regulatory framework prohibits biopharmaceutical manufacturers—and only them—from sharing truthful and non-misleading information about available treatments. In Section II, we discuss how FDA's current interpretation of its regulatory framework is inconsistent with First Amendment jurisprudence and explain recent developments in this area. In Section III, we explore how both patient and provider groups are actively participating in discussions regarding the reform of FDA's regulatory framework and requesting policies promoting enhanced sharing of data-driven information between biopharmaceutical companies and healthcare professionals. Finally, in Section IV, we offer suggestions for a new regulatory paradigm to allow FDA to regulate medical communications that will enhance the availability of truthful, non-misleading information to healthcare professionals, preserve FDA's critical role in approving new drugs and their use and comport with strictures of the First Amendment.

## I. BACKGROUND

### A. *Physicians Require Accurate, Data-Driven Information About the Medicines They Prescribe*

In 2013, retail pharmacies filled over three billion prescriptions.<sup>4</sup> These prescriptions, as well as those prescriptions administered directly by healthcare professionals, were intended to treat or prevent myriad conditions and diseases, because physicians can lawfully prescribe FDA-approved products for any purpose, including uses unapproved by FDA, if the physician believes such use would benefit the patient.<sup>5</sup> Because almost all prescription medicines have side effects and contraindications, including some serious and fatal side effects, it is essential that healthcare professionals have access to timely, accurate and comprehensive information about the medicines they prescribe.

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uses of FDA-approved medicines, (3) information pertaining to non-medically approved investigational uses of FDA-approved medicines, or (4) information about strictly investigational medicines that have not been approved by FDA for any use. Here we focus on information relating to the first two categories.

<sup>4</sup> *Total Number of Retail Prescription Drugs Filled at Pharmacies*, KAISER FAM. FOUND., <http://kff.org/other/state-indicator/total-retail-rx-drugs/> (last visited Jan. 27, 2015).

<sup>5</sup> *Buckman Co. v. Plaintiffs' Legal Comm.*, 531 U.S. 341, 350 (2001).

It is imperative that providers have that information to be able to balance the benefits and risks of different treatment options for each individual patient.<sup>6</sup>

Healthcare professionals learn about prescription drugs through a variety of sources, such as lectures and continuing medical education (CME) symposia, advertising and labeling, FDA-approved prescribing information (PI), medical literature including peer-reviewed journals, professional meetings, and social media.<sup>7</sup> Materials created by and/or distributed by any individual or entity other than the manufacturer of the medicine are likely to contain information supported by data collected in a variety of ways and discuss numerous uses for the product. For example, data to support optimal uses of medicines for a particular patient may be obtained from different clinically valuable mechanisms, including meta-analyses, real world evidence (e.g., health records, payer data), observational studies, and sub-population analyses (e.g., results based on gender).<sup>8</sup> Moreover, many of these sources typically contain some information about both approved uses and medically accepted alternative uses of FDA-approved medicines.<sup>9</sup> Manufacturers of innovative medical treatments would be expected to collect the most up-to-date, comprehensive information about their treatments; yet, as described below, they are nevertheless restricted from sharing much of the information they collect with trained healthcare professionals.

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<sup>6</sup> Furthermore, although somewhat beyond the scope of this article, it is also critical that payers, formulary committees, and other similar individuals and entities have access to healthcare economic information so that they can make informed decisions about drug coverage and reimbursement. See Letter from James M. “Mit” Spears, Exec. Vice President & Gen. Counsel, Pharm. Research & Mfrs. of Am., to Margaret Hamburg, Comm’r, Food & Drug Admin., The Development and Dissemination of Health Care Economic Data to Payers, Formulary Committees, or Other Similar Entities (Aug. 14, 2012).

<sup>7</sup> Increasingly, physicians are using the Internet and social media to facilitate their daily practice. A 2012 survey found that about 24% of doctors use social media on at least a daily basis to research and review medical information and about 61% monitor social media on a weekly basis. Brian S. McGowan et al., *Understanding the Factors that Influence the Adoption and Meaningful Use of Social Media by Physicians to Share Medical Information*, 14 J. OF MED. INTERNET RES. e117 (2012), available at <http://www.jmir.org/2012/5/e117/>. Only twenty-three of the top fifty global pharmaceutical companies, however, regularly use such media. Press Release: *IMS Health: Pharma Should Make Better Use of Social Media to Engage Patients and Improve the Use of Medicines*, IMS INST. FOR HEALTHCARE INFORMATICS (Jan. 21, 2014), <http://www.imshealth.com/vgn-ext-templating/v/index.jsp?vgnextoid=ebc072cc270b3410VgnVCM10000076192ca2RCRD>.

<sup>8</sup> This is a non-exhaustive list of potentially clinically valuable scientific information. FDA has recognized the importance of these types of mechanisms in the preamble to 21 C.F.R. part 99, implementing Section 401 of the Food and Drug Administration Modernization Act of 1997 (FDAMA). In the preamble to the final rule, FDA noted that it intended to permit dissemination of materials describing new uses of approved drugs, including “historically controlled studies, retrospective analyses, open label studies, and meta-analyses if they are testing a specific clinical hypothesis.” Dissemination of Information on Unapproved/New Uses for Marketed Drugs, Biologics, and Devices, 64 Fed. Reg. 64,556, 64,559 (Nov. 20, 1998). Section 401 of FDAMA and the implementing regulations at 21 C.F.R. part 99 sunset on September 30, 2006. See FOOD & DRUG ADMIN., DRAFT GUIDANCE FOR INDUSTRY: DISTRIBUTING SCIENTIFIC AND MEDICAL PUBLICATIONS ON UNAPPROVED NEW USES—RECOMMENDED PRACTICES 5 (2014) [hereinafter DRAFT GUIDANCE: PUBLICATIONS ON UNAPPROVED NEW USES], available at <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm387652.pdf>.

<sup>9</sup> *Testimony*, *supra* note 2 (“The National Cancer Institute’s Physician Data Query (PDQ) system is an excellent source for oncologists to obtain information about current oncologic therapies. The National Library of Medicine (NLM) offers a Medical Literature Analysis and Retrieval System (MEDLARS), which is a computerized system of databases and databanks pertinent to biomedical research and patients. . . . FDA does not regulate a physician’s access to any of these sources of independent off-label use information —no matter how preliminary the data may be.”).

B. *FDA's Current Regulatory Scheme Severely Restricts the Dissemination of Accurate, Data-Driven Information about Approved Uses of FDA-Approved Drugs and Medically Accepted Alternative Uses of FDA-Approved Drugs*

While all other individuals and entities may freely discuss and exchange information about both approved uses and alternative uses of FDA-approved medicines, the Agency—through its current interpretation of the Federal Food, Drug, and Cosmetic Act (FDCA)—significantly limits biopharmaceutical companies' ability to communicate proactively about the medicines they research, develop, and bring to patients. As we describe in this section, this is so even for information or data about approved uses that is not contained within FDA-approved labeling as well as alternative uses that are lawfully prescribed, the medical standard of care, and reimbursed by the federal government. Companies develop and gather a wealth of information about their approved products by conducting meta-analyses of study data, analyzing pharmacoeconomic or comparative cost data, assessing sub-population information, and collecting real world evidence—many of the same sources of information for materials that are distributed to healthcare professionals by other individuals and entities.<sup>10</sup> Although such data may be accumulated by companies to satisfy FDA approval and post-approval safety monitoring requirements, drive new research and innovation, or enhance scientific knowledge and understanding of medicines, companies are often prohibited from sharing the information with healthcare professionals.

Under the FDCA, a biopharmaceutical manufacturer must submit to FDA, and FDA must approve, a detailed application for a new drug that includes information supporting its safety and effectiveness and proposed labeling, before the company may legally market the drug.<sup>11</sup> FDA will approve a new drug application only if, among other things: (1) there is sufficient “information to determine whether such drug is safe for use under such conditions;”<sup>12</sup> (2) there is “substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling thereof,” which generally requires support by two adequate and well-controlled clinical trials;<sup>13</sup> and (3) the proposed labeling is not “false or misleading in any particular.”<sup>14</sup> FDA approval is only for those uses “prescribed, recommended, or suggested,” in the approved labeling, and a manufacturer must submit a supplemental new drug application and obtain approval for an amendment to the

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<sup>10</sup> See Letter from Martha Nolan, Vice President, Pub. Policy, Soc’y for Women’s Health Research to the Honorable Fred Upton, Chairman, Comm. on Energy & Commerce and the Honorable Diane DeGette, Comm. on Energy & Commerce, on the 21st Century Cures Initiative—A Patient Advocacy Perspective (June 9, 2014) [hereinafter Letter from Nolan], available at <http://energycommerce.house.gov/sites/republicans.energycommerce.house.gov/files/analysis/21stCenturyCures/20140707PatientWhitePaperResponses.pdf> (pages 10–12 of linked PDF).

<sup>11</sup> 21 U.S.C. § 355(a), (b)(1)–(2) (2012). The FDCA states that “[n]o person shall introduce or deliver for introduction into interstate commerce any new drug, unless an approval of an application . . . is effective with respect to such a drug.” *Id.* § 355(a).

<sup>12</sup> *Id.* § 355(d)(4).

<sup>13</sup> *Id.* § 355(d)(5). In some limited instances, the data from one adequate and well-controlled clinical investigation may constitute substantial evidence that “the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof.” *Id.* § 355(d)(5); see also 21 C.F.R. §§ 201.56(a)(3), 201.57(c)(2)(iv), (v), 314.126 (2014); FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY: PROVIDING CLINICAL EVIDENCE OF EFFECTIVENESS FOR HUMAN DRUG AND BIOLOGIC PRODUCTS 3–4 (1998), available at <http://www.fda.gov/downloads/Drugs/.../Guidances/ucm078749.pdf>.

<sup>14</sup> 21 U.S.C. § 355(d).

labeling that adds additional recommended or suggested uses of the product.<sup>15</sup> While the FDCA only defines “label” and “labeling” to include “written, printed, or graphic matter,”<sup>16</sup> FDA has broadly interpreted the term “labeling” to include essentially all communications made by a manufacturer.<sup>17</sup>

A drug is misbranded, among other things, if its labeling is “false or misleading in any particular” or lacks “adequate directions for use.”<sup>18</sup> To determine if labeling is misleading, FDA and courts consider (A) affirmative statements made by the manufacturer and (B) a manufacturer’s failure to reveal material facts (i) in light of other representations made or suggested or (ii) with respect to consequences which may result from use of the medicine under the conditions prescribed in such labeling or under such conditions of use that are customary or usual.<sup>19</sup> Historically, FDA has warned that company communications about medicines may be misleading if a claim is not supported by the “substantial evidence” standard required for drug approval. Because FDA deems virtually any communication by a company to be labeling, the Agency believes that a biopharmaceutical company may communicate information about a medicine only if such speech is supported by the “substantial evidence” requirement for new drug application approvals.<sup>20</sup> That is, under FDA’s view, any information disseminated by a manufacturer about an approved product typically must be supported by at least two adequate and well-controlled clinical trials.<sup>21</sup> Thus, FDA now also uses its evidentiary standard for drug approval as its standard for determining whether information about a medicine may deem it misbranded.

Failure to comply with FDA’s approval and labeling requirements can result in the government bringing criminal charges against a manufacturer under a variety of different theories. Specifically, the FDCA prohibits introducing a new drug into interstate commerce that has not been approved by FDA<sup>22</sup> and introducing a “misbranded” drug into interstate commerce.<sup>23</sup> FDA has taken an overly expansive interpretation of these

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<sup>15</sup> 21 U.S.C. § 321(p)(1); 21 C.F.R. § 314.70.

<sup>16</sup> “Label” is statutorily defined as “a display of written, printed, or graphic matter upon the immediate container of any article.” 21 U.S.C. § 321(k). “Labeling” is statutorily defined as “all labels and other written, printed, or graphic matter (1) upon any article or any of its containers or wrappers, or (2) accompanying such article.” *Id.* § 321(m). See *Kordel v. United States*, 335 U.S. 345 (1948) (interpreting the statutory term “labeling”).

<sup>17</sup> 21 C.F.R. § 202.1(l)(2) (“Brochures, booklets, mailing pieces, detailing pieces, file cards, bulletins, calendars, price lists, catalogs, house organs, letters, motion picture films, film strips, lantern slides, sound recordings, exhibits, literature, and reprints and similar pieces of printed, audio, or visual matter descriptive of a drug and references published (for example, the ‘Physicians Desk Reference’) for use by medical practitioners, pharmacists, or nurses, containing drug information supplied by the manufacturer, packer, or distributor of the drug and which are disseminated by or on behalf of its manufacturer, packer, or distributor are hereby determined to be labeling as defined in section 201(m) of the act.”); see also David A. Kessler & Wayne L. Pines, *The Federal Regulation of Prescription Drug Advertising and Promotion*, 264 JAMA 2409 (1990).

<sup>18</sup> 21 U.S.C. § 352(a), (f)(1).

<sup>19</sup> 21 U.S.C. § 321(m); 21 C.F.R. § 1.21.

<sup>20</sup> See, e.g., Warning Letter from Food & Drug Admin. Office of Prescription Drug Promotion to Larry Downey, Exec. Vice President, Teva Pharm. USA (Mar. 14, 2012), available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/EnforcementActivitiesbyFDA/WarningLettersandNoticeofViolationLettersstoPharmaceuticalCompanies/UCM296204.pdf> (FDA stated that “[p]romotional materials are misleading if they suggest that a drug is more effective or useful in a broader range of conditions or patients than has been demonstrated by substantial evidence or substantial clinical experience.”).

<sup>21</sup> 21 U.S.C. § 355(d).

<sup>22</sup> *Id.* §§ 331(d), 355(a).

<sup>23</sup> *Id.* §§ 331(a), 352.

provisions and has interpreted them to support a finding that a manufacturer introduces a new drug and/or misbrands a drug when it references information about a medicine that is not within the scope of FDA's approved labeling.<sup>24</sup> These same references to information outside of the approved labeling can serve as a basis for False Claims Act liability.<sup>25</sup>

Likewise, FDA has found that a drug is misbranded if the manufacturer makes a statement suggesting that the drug is safe and effective for a use that has not been approved by FDA.<sup>26</sup> FDA frequently uses both the "adequate directions for use" and "intended use" regulations to reach this conclusion.<sup>27</sup> The regulations require that labeling include adequate directions not only for approved uses of a product but also for intended uses of the product,<sup>28</sup> and FDA broadly defines "intended use" to include the manufacturers' objective intent, which FDA believes can be "determined from its label, accompanying labeling, promotional claims, advertising and any other relevant source."<sup>29</sup>

Hence, if a manufacturer provides truthful and non-misleading information about an alternative use of its approved drug, FDA's regulations require that the manufacturer provide "adequate directions" for that use in the "labeling" to protect against a misbranding charge.<sup>30</sup> Short of compiling a new marketing application and waiting for FDA approval, the manufacturer is unable to make these labeling changes and comply with that requirement, however, because labeling can address only the approved uses of the drug. FDA's interpretation of the FDCA thus creates a Catch-22: If a manufacturer tries to avoid a misbranding charge by updating its labeling to include adequate directions

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<sup>24</sup> *Id.* §§ 331(a), 352.

<sup>25</sup> See, e.g., *Justice Department Recovers \$3.8 Billion from False Claims Act Cases in Fiscal Year 2013*, U.S. DEPARTMENT OF JUST. (Dec. 20, 2013), <http://www.justice.gov/opa/pr/justice-department-recovers-38-billion-false-claims-act-cases-fiscal-year-2013> (noting False Claims Act settlements for alleged "off-label marketing" in violation of the FDCA).

<sup>26</sup> See also Warning Letter from Food & Drug Admin. Div. of Drug Mktg., Adver. & Comm'ns to Francois Fournier, CEO, Galderma Labs. (Aug. 18, 2009), available at <http://www.fda.gov/downloads/drugs/ucm179836.pdf>.

<sup>27</sup> See Warning Letter from Food & Drug Admin. Office of Prescription Drug Promotion to Marc Beer, CEO, Aegerion Pharm., Inc. (Nov. 8, 2013), available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/EnforcementActivitiesbyFDA/WarningLettersandNoticeofViolationLettersToPharmaceuticalCompanies/UCM374338.pdf>; see also *United States v. Caronia*, 703 F.3d 149, 165 (2d Cir. 2012); Letter from Leslie Kux, Assistant Comm'r for Policy, Food & Drug Admin., to Med. Info. Working Grp. (MIWG) on Dockets Nos. FDA-2011-P-0512 and FDA-2013-P-1079 (June 6, 2014) [hereinafter Letter from Kux], available at [http://fcablog.sidley.com/files/Uploads/Documents/FCA/FDA%20Response%20to%202011%20and%202013%20CP%20\(June%206,%202014\).pdf](http://fcablog.sidley.com/files/Uploads/Documents/FCA/FDA%20Response%20to%202011%20and%202013%20CP%20(June%206,%202014).pdf).

<sup>28</sup> 21 C.F.R. § 201.100(c)(1) (2014) (explaining that a drug is exempt from misbranding if "[l]abeling on or within the package from which the drug is to be dispensed bears adequate information for its use . . . under which practitioners licensed by law to administer the drug can use the drug safely and for the purposes for which it is intended, including all purposes for which it is advertised or represented").

<sup>29</sup> DRAFT GUIDANCE: PUBLICATIONS ON UNAPPROVED NEW USES, *supra* note 8, at 4 (citing *Action on Smoking and Health v. Harris*, 655 F.2d 236, 239 (D.C. Cir. 1980)); see also 21 C.F.R. § 201.128 (2014).

<sup>30</sup> The government has articulated its "misbranding" theory as follows: "The [Act], at 21 U.S.C. § 352(f)(1), provided that a drug was misbranded if, among other things, the labeling did not contain adequate directions for use." As the phrase was used in the [Act], "adequate directions for use" could not be written for medical indications or uses for which the drug had not been proven to be safe and effective, through well-controlled clinical studies. Any uses for a drug that were not approved by FDA as safe and effective, and thus that were not included in the drug's approved labeling, were known as "off-label" indications or uses. A drug that was promoted for an off-label indication or use did not contain "adequate directions for use," because such an off-label indication or use was not included in FDA-approved labeling for the drug, and that drug was therefore misbranded under Section 352(f)." Trial Pleading at 2, *United States v. Cephalon, Inc.*, No. 08-598, (E.D. Pa. Sept. 29, 2008), 2008 WL 4498615.

for use, then the product is deemed by FDA to be a “new drug” that must be approved before being marketed to the public.<sup>31</sup>

### C. *FDA has Acknowledged the Importance of Using FDA-Approved Medicines for Medically Accepted Alternative Uses and Federal Healthcare Programs Often Provide Reimbursements for Such Uses*

Although a manufacturer’s communications about alternative uses of FDA-approved products may be criminalized, the *prescribing* of an approved product by a healthcare professional for an unapproved use is a common, lawful medical practice that often represents the standard of care.<sup>32</sup> In many instances, federal law even requires the government to reimburse the provider when FDA-approved drugs are prescribed for medically accepted alternative uses.<sup>33</sup> FDA also has acknowledged the benefit of prescribing approved products for alternative uses on multiple occasions in a variety of different forums. For example, in a draft guidance document, FDA has previously noted 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.”<sup>34</sup> FDA officials have also made similar statements in congressional testimony and public speeches.<sup>35</sup>

<sup>31</sup> 21 U.S.C. §§ 321(p), 355(a) (2012).

<sup>32</sup> Over twenty percent of prescriptions are written for an unapproved use. David C. Radley et al., *Off-Label Prescribing Among Office-Based Physicians*, 166 ARCHIVES INTERNAL MED. 1021, 1023 (2006). The percentage of prescriptions written for unapproved uses is even greater in some fields of medicine such as pediatrics and oncology. Paolo Casali, *The Off-Label Use of Drugs in Oncology: A Position Paper by the European Society for Medical Oncology (ESMO)*, 18 ANNALS ONCOLOGY 1923, 1923 (2007).

<sup>33</sup> Federal law requires that both the Medicare and Medicaid programs provide reimbursements for prescriptions for unapproved uses of FDA-approved products if the use is “medically accepted.” For the purposes of reimbursement decisions under the Medicaid program, the term “medically accepted” means that FDA has approved the drug for that use, or in the alternative, the use is cited in one or more of three specified drug compendia (i.e., the American Hospital Formulary Service Drug Information, United States Pharmacopeia-Drug Information, and the DrugDex® Information System). See 42 U.S.C. § 1396r-8(d)(1)(B)(i), (d)(4)(C) (2012) (Medicaid); see also 42 U.S.C. § 1395x(t). Under the Medicare outpatient drug program, a drug may be covered in some instances even though it is *not* being prescribed for an FDA-approved use or a use listed in any of the statutorily identified compendia. See *Layzer v. Leavitt*, 770 F. Supp. 2d 579 (S.D.N.Y. 2011).

<sup>34</sup> “Off-Label” and Investigational use of Marketed Drugs, Biologics, and Medical Devices—*Information Sheet*, FOOD & DRUG ADMIN., <http://www.fda.gov/RegulatoryInformation/Guidances/ucm126486.htm> (last updated June 25, 2014); see also FOOD & DRUG ADMIN., DRAFT GUIDANCE FOR INDUSTRY: RESPONDING TO UNSOLICITED REQUESTS FOR OFF-LABEL INFORMATION ABOUT PRESCRIPTION DRUGS AND MEDICAL DEVICES 55–56 (2011) [hereinafter DRAFT GUIDANCE: RESPONDING TO UNSOLICITED REQUESTS FOR OFF-LABEL INFORMATION], available at <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm285145.pdf>; *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*, FOOD & DRUG ADMIN. (Jan. 2009), <http://www.fda.gov/RegulatoryInformation/Guidances/ucm125126.htm> (last updated June 25, 2014).

<sup>35</sup> See *More Information for Better Patient Care: Hearing on S.1477 Before the S. Comm. on Labor and Human Resources*, 104th Cong. 81 (1996) (statement of William B. Shultz, then-Deputy Commissioner for Policy, FDA) (“FDA knows that there are important off label uses of approved drugs. In this context, it is important that physicians have access to accurate information about drugs.”); Carol Scheman, *Prescription Drug Marketing and Promotion—An FDA Perspective*, Address before the PMA Public Affairs Section, Mid-Year Meeting (April 1992) (acknowledging as then-Deputy Commissioner for External Affairs that using FDA-approved products for unapproved uses is often essential—and sometimes necessary—to medical practice and can help ensure “that science and medicine move forward to benefit patients with intractable illness”); Stuart J. Nightingale, *Unlabeled Uses of Approved Drugs*, 26 DRUG INFO. J. 141, 145 (1992);

More recently, however, FDA has taken a step backwards and, without justification, revised some of its earlier statements, demonstrating an apparent reluctance to acknowledge the prevalence and importance of medically appropriate prescription of medicines for unapproved uses to patient care.<sup>36</sup> But even in these instances, FDA ultimately has recognized that healthcare professionals benefit from receiving truthful and non-misleading information about alternative uses through publications such as scientific and medical publications.<sup>37</sup> In June 2014, in its response to a citizen's petition, FDA acknowledged that "for some health conditions, off-label uses of medical products have made valuable contributions to patient care" and that "there can be utility in the dissemination of truthful and non-misleading scientific or medical information regarding off-label uses under appropriate circumstances."<sup>38</sup>

*D. FDA Has Not Provided A Clear Safe Harbor for Companies to Share Truthful, Non-Misleading Information with Healthcare Professionals When Such Information Falls Outside of the Package Insert*

Although FDA has issued regulations, guidance documents, and policies to facilitate the dissemination of certain truthful and non-misleading information about approved uses and medically accepted alternative uses of approved products, FDA has not provided manufacturers with a meaningful safe harbor that enables them to share accurate, data-driven information with healthcare professionals.<sup>39</sup> For example, in draft guidance entitled "Responding to Unsolicited Requests for Off-Label Information About Prescription Drugs and Devices," FDA acknowledged that "[s]cientific or medical departments within drug or medical device firms often maintain a large body of information about their products," which often includes the most accurate and up-to-date information that may not be available to other entities.<sup>40</sup> In the same guidance, however, the Agency imposed arbitrary, confusing distinctions regarding whether a biopharmaceutical company can communicate scientifically accurate, truthful and non-misleading information about alternative uses of approved products, thereby limiting its usefulness and running afoul of the First Amendment.<sup>41</sup> For example, FDA has articulated

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*Testimony, supra* note 2, at 3 (statement of Michael Friedman, then-Deputy Commissioner for Operations, Food & Drug Admin.).

<sup>36</sup> DRAFT GUIDANCE: PUBLICATIONS ON UNAPPROVED NEW USES, *supra* note 8.

<sup>37</sup> *Id.* at 6.

<sup>38</sup> Letter from Kux, *supra* note 27, at 7.

<sup>39</sup> FDA has acknowledged its failure to provide clear guidance. In the aforementioned citizen petition submitted by the Medical Information Working Group (MIWG), FDA noted that "there is a lack of clarity regarding truthful, non-misleading scientific communications and activities related to investigational new drugs and investigational devices and off-label uses of marketed drugs and devices," FDA agreed to review FDA's regulations, guidance, and policies in light of First Amendment case law. *See* Medical Information Working Group (MIWG) Citizen Petition, Docket No. FDA-2013-P-1079, at 2, 5 (Sept. 3, 2013); Letter from Kux, *supra* note 27, at 2.

<sup>40</sup> FOOD & DRUG ADMIN., DRAFT GUIDANCE FOR INDUSTRY: RESPONDING TO UNSOLICITED REQUESTS FOR OFF-LABEL INFORMATION ABOUT PRESCRIPTION DRUGS AND DEVICES 2, 10 (2011), available at <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm285145.pdf>. Similarly, FDA's 1997 final guidance entitled "Industry-Supported Scientific and Educational Activities," and the 2014 revised draft guidance entitled "Distributing Scientific and Medical Publications on Unapproved New Uses," do not provide industry with clear guidelines on how to share information about approved uses and unapproved uses of FDA-approved products. *See* FDA, Final Guidance for Industry: Industry-Supported Scientific and Educational Activities (Nov. 1997).

<sup>41</sup> For example, the Agency distinguished between "solicited" and "unsolicited" requests for information about unapproved uses of approved drugs and states that manufacturers may only respond to "unsolicited

a dichotomy between public and private unsolicited requests for information about alternative uses and recommends that, for public unsolicited requests, manufacturers: (1) only respond to requests that specifically identify the manufacturer's product; (2) limit the public response to providing contact information for specific departments and only provide detailed answers after being privately contacted; (3) disclose the involvement with the firm of the representative who answers the request; and (4) not include any promotional materials.<sup>42</sup> Distinguishing between public and private requests for information was unprecedented and contradicted previous statements made by FDA officials.<sup>43</sup>

## II. FDA'S CURRENT REGULATORY FRAMEWORK IS INCONSISTENT WITH FIRST AMENDMENT JURISPRUDENCE

### A. Overview of Relevant First Amendment Jurisprudence

The First Amendment forbids Congress from making any law "abridging the freedom of speech."<sup>44</sup> In 2011, the Supreme Court affirmed the principle that "speech in aid of pharmaceutical marketing . . . is a form of expression protected by the Free Speech Clause of the First Amendment" and acknowledged that the First Amendment serves an essential function "in the fields of medicine and public health, where information can save lives."<sup>45</sup> In this case and other recent decisions, courts have enhanced the protections for speech regulated by FDA. Thus, as one scholar has concluded, the Agency "faces an increasing and very high burden in any effort to regulate company speech."<sup>46</sup>

The landmark test for evaluating restrictions on commercial speech was established in *Central Hudson Gas & Electric Corporation v. Public Service Commission of New York*.<sup>47</sup> In general, the First Amendment permits restrictions on commercial speech only if: (1) the speech at issue concerns unlawful activity or is inherently false or misleading;<sup>48</sup>

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requests." Furthermore, FDA discussed public versus private unsolicited requests for information and imposes arbitrary restrictions on a biopharmaceutical company's ability to respond to public unsolicited requests. DRAFT GUIDANCE: RESPONDING TO UNSOLICITED REQUESTS FOR OFF-LABEL INFORMATION, *supra* note 34, at 2, 3, 10–12; see 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, 319 (2011).

<sup>42</sup> Similarly, the Agency distinguished between "solicited" and "unsolicited" requests for information about unapproved uses of approved drugs and states that manufacturers may only respond to "unsolicited requests." DRAFT GUIDANCE: RESPONDING TO UNSOLICITED REQUESTS FOR OFF-LABEL INFORMATION, *supra* note 34, at 2, 3, 10–12; see 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, 319 (2011).

<sup>43</sup> See Comment Letter from Pharm. Research & Mfrs. of Am. (PhRMA), to Food & Drug Admin., on Draft Guidance for Industry: Responding to Unsolicited Requests for Off-Label Information About Prescription Drugs and Devices, Docket No. FDA-2011-D-0868 (Mar. 28, 2012) (on file with author and with Food & Drug Law Journal) (citing testimony of FDA official in *United States v. Stevens*, No. RWT-10-694 (D. Md. Apr. 27, 2011) (FDA official testified that a physician being paid by a biopharmaceutical company could provide a comprehensive public answer about unapproved uses of FDA-approved products to a group of physicians if done so in response to unsolicited questions from the group)).

<sup>44</sup> U.S. CONST. amend. I.

<sup>45</sup> *Sorrell v. IMS Health, Inc.*, 131 S. Ct. 2653, 2659, 2664 (2011).

<sup>46</sup> Ralph F. Hall, *Is Caronia the Most Important FDA Related Judicial Decision of Our Generation?*, FOOD & DRUG POL'Y F., Aug. 28, 2013, at 1, 9.

<sup>47</sup> 447 U.S. 557, 566 (1980). First Amendment protections were first extended to commercial speech in *Virginia Board of Pharmacy v. Virginia Citizens Consumer Council*, 425 U.S. 748, 761–62 (1976).

<sup>48</sup> The phrase "misleading" as used in the framework established in *Central Hudson* has been interpreted as meaning "inherently misleading." In re R.M.J., 455 U.S. 191, 203 (1982). "Potentially misleading"

or (2) the restriction directly furthers a substantial governmental interest, and the restriction is no more extensive than necessary to serve that interest.<sup>49</sup> The restriction on speech must provide more than “ineffective or remote support for the government’s purpose,” and is not permissible if the government’s interest could be “served as well by a more limited restriction.”<sup>50</sup>

In the thirty-five years since *Central Hudson*, the Supreme Court has enhanced its protection of commercial speech and reduced its tolerance for claims alleging that a legitimate substantial government interest is served by censoring truthful and non-misleading speech.<sup>51</sup> Moreover, there have been numerous First Amendment challenges to FDA’s approach regarding manufacturer communications about its FDA-approved products.<sup>52</sup> In response to these cases, especially those where the government’s speech restrictions were deemed to be unconstitutional, the Agency acknowledged that the First Amendment was implicated by some of its restrictions and solicited public comment on how “to ensure that [FDA’s] regulations, guidances, policies, and practices . . . comply with the governing First Amendment case law.”<sup>53</sup>

Two recent cases have highlighted the First Amendment difficulties FDA faces with respect to the Agency’s current interpretation of its authority under the FDCA to curtail truthful, non-misleading speech by biopharmaceutical companies. *Sorrell v. IMS Health*<sup>54</sup> established, and *United States v. Caronia*<sup>55</sup> confirmed, that content- and speaker-based restrictions are subject to heightened scrutiny regardless of whether the restricted speech is commercial or non-commercial in nature.<sup>56</sup> In *Sorrell*, the Supreme Court invalidated a Vermont law prohibiting biopharmaceutical manufacturers or marketers from engaging in the sale, disclosure, and use of doctors’ prescribing history for the purpose of pharmaceutical marketing, unless the doctor expressly permitted the use of such data.<sup>57</sup> The Court noted that “heightened scrutiny” applied because the law was “directed at certain content and [was] aimed at particular speakers.”<sup>58</sup> Because the law also failed the more traditional commercial speech inquiry under *Central Hudson*, however, the Court did not further elaborate on the heightened scrutiny standard, because it was not a necessary piece of the Court’s inquiry.<sup>59</sup>

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commercial speech is still entitled to First Amendment protection. *Id.*

<sup>49</sup> *Cent. Hudson Gas & Elec. Corp.*, 447 U.S. at 566.

<sup>50</sup> *Id.* at 564.

<sup>51</sup> See *Lorillard Tobacco Co. v. Reilly*, 533 U.S. 525, 564 (2001); *Greater New Orleans Broad. Ass’n, Inc. v. United States*, 527 U.S. 173, 195–96 (1999); *44 Liquormart, Inc., v. Rhode Island*, 517 U.S. 484, 510 (1996).

<sup>52</sup> See generally *Thompson v. W. States Med. Ctr.*, 535 U.S. 357, 373 (2002); *Pearson v. Shalala*, 164 F.3d 650, 654 (D.C. Cir. 1999); *Wash. Legal Found. v. Henney*, 56 F. Supp. 2d 81, 87 (D.D.C. 1999); *Wash. Legal Found. v. Friedman*, 13 F. Supp. 2d 51, 66 (D.D.C. 1998); Krista Hessler Carver, *A Global View of the First Amendment Constraints on FDA*, 63 *FOOD & DRUG L.J.* 151, 179–86 (2008); Gerald Masoudi & Christopher Pruitt, *The Food and Drug Administration v. the First Amendment: A Survey of Recent FDA Enforcement*, 21 *HEALTH MATRIX* 111, 123–28 (2011).

<sup>53</sup> Carver, *supra* note 52, at 152 (quoting Request for Comment on First Amendment Issues, 67 *Fed. Reg.* 34,942, 34,942 (May 16, 2002)).

<sup>54</sup> 131 S. Ct. 2653 (2011).

<sup>55</sup> 703 F.3d 149 (2d Cir. 2012).

<sup>56</sup> See *Sorrell v. IMS Health, Inc.*, 131 S. Ct. 2653, 2665 (2011); *United States v. Caronia*, 703 F.3d 149, 162–63 (2d Cir. 2012).

<sup>57</sup> *Sorrell*, 131 S. Ct. at 2659–60.

<sup>58</sup> *Id.* at 2664–65.

<sup>59</sup> *Id.* at 2667. Given the analysis in *Sorrell*, it appears that very few content—or speaker—based regulations would survive heightened scrutiny when there is a viable regulatory alternative, such as providing additional disclosures about a given communication. The Supreme Court alluded to this fact in *Sorrell* when

In *Caronia*, the Second Circuit held that interpreting the FDCA's misbranding provisions to prohibit manufacturers' truthful and non-misleading communication about alternative uses of FDA-approved medicines would violate the First Amendment.<sup>60</sup> In this case, Alfred Caronia, a sales representative for Jazz Pharmaceuticals, was convicted of conspiracy to introduce a misbranded drug into interstate commerce. The government had obtained audio recordings of him discussing alternative uses of a Jazz medicine, Xyrem, with physicians. Importantly, the government did not claim that the speech itself was false or misleading. On appeal, the Second Circuit concluded that the government's interpretation of the FDCA's misbranding provisions should be subject to heightened scrutiny under *Sorrell*; because it imposed content-based (i.e., it "distinguish[ed] between 'favored speech' and 'disfavored speech on the basis of the ideas or views expressed'") and speaker-based (i.e., it "target[ed] one kind of speaker—pharmaceutical manufacturers—while allowing others to speak without restriction") distinctions.<sup>61</sup>

Similar to the approach taken in *Sorrell*, after establishing that heightened scrutiny applied, the court did not elaborate on the heightened standard because the speech restrictions at issue did not even pass constitutional muster under the intermediate standard of review established in *Central Hudson*. The court noted that prohibiting manufacturer speech about alternative uses does not "directly further the government's goals of preserving the efficacy and integrity of FDA's drug approval process and reducing patient exposure to unsafe and ineffective drugs."<sup>62</sup> The government's construction of the FDCA "essentially legalizes the outcome—off-label use—but prohibits the free flow of information that would inform that outcome."<sup>63</sup> The court reasoned that the government's goals were not directly advanced because other individuals and entities can continue to share information about these uses, and such uses of approved products continues to be lawful.<sup>64</sup>

### B. *Constitutional Analysis of FDA's Criminalization of Truthful and Non-Misleading Speech about Approved Uses and Medically Accepted Alternative Uses of FDA-Approved Drugs*

Because FDA's "labeling," "substantial evidence," and "intended use" regulations potentially criminalize truthful, and non-misleading communication about approved uses and medically accepted alternative uses of approved products, they chill manufacturers from sharing accurate, data-driven information about approved products that would enhance physician understanding about the medicines they prescribe. A cursory analysis demonstrates that FDA's current interpretation of these regulations and policies violates the First Amendment under both heightened scrutiny, which is warranted for content- and

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it noted that "[i]n the ordinary case [not involving an issue of commercial speech] it is all but dispositive to conclude that a law is content-based, and in practice, viewpoint-discriminatory." *Id.* Similarly, since *Sorrell*, some courts have discussed the difficulty over overcoming speaker-based and content-based restrictions in the context of commercial speech. *See Valle Del Sol Inc. v. Whiting*, 709 F.3d 808, 825 (9th Cir. 2013); *Nat'l Ass'n of Tobacco Outlets, Inc. v. Worcester*, 851 F. Supp. 2d 311, 319 (D. Mass. 2012).

<sup>60</sup> *United States v. Caronia*, 703 F.3d 149, 168–69 (2d Cir. 2012).

<sup>61</sup> *Id.* at 165.

<sup>62</sup> *Id.* at 166. The court also acknowledged that 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." *Id.* at 167 (internal citation omitted).

<sup>63</sup> *Id.* at 167.

<sup>64</sup> *Id.*

speaker-based restrictions on commercial speech, and the more traditional commercial speech analysis established in *Central Hudson*. Indeed, the aforementioned cases, *Sorrell* and *Caronia*, provide a strong foundation for a challenge to FDA's regulations under both heightened and intermediate scrutiny.

FDA's regulations are speaker- and content-based restrictions on speech, because they only apply to biopharmaceutical companies and to speech about pharmaceuticals. Perversely, only the company that researches and develops a new medicine is prohibited from sharing all of the information it has about the treatment in a truthful, non-misleading manner. Only a manufacturer can be held liable for introducing a new drug into interstate commerce or introducing a misbranded drug into interstate commerce under FDA's "labeling," "substantial evidence," and "intended use" regulations when it disseminates truthful and non-misleading information. Precisely the same speech is lawful if made by *any* other speaker, such as a doctor, nurse, or insurance company representative. Indeed, physicians and medical journals "routinely discuss off-label uses, comparative effectiveness, and other topics subject to FDA regulation."<sup>65</sup>

Furthermore, even if an intermediate level of scrutiny were applied under the commercial speech doctrine, FDA's restrictive regulations on biopharmaceutical companies' truthful and non-misleading speech about approved uses and medically accepted alternative uses of FDA-approved medicines would not pass constitutional muster. It is unlikely that FDA can show that its restrictions on truthful, non-misleading communication directly advance a substantial government interest, or that the restrictions are the least-restrictive alternative.<sup>66</sup> Although the government typically is able to identify a substantial governmental interest in First Amendment cases,<sup>67</sup> it becomes more problematic when the government's interests are premised on a "paternalistic notion that physicians, a sophisticated audience, cannot evaluate the validity of promotional materials."<sup>68</sup> As noted by the *Sorrell* Court, "the fear that people would make bad decisions if given truthful information' cannot justify content-based burdens on speech," especially "when the audience . . . consists of 'sophisticated and experienced' consumers."<sup>69</sup> After *Caronia*, it seems even less likely that the government may successfully argue that a substantial governmental interest is directly advanced by FDA's restrictions on manufacturer speech because, as previously discussed and as noted by the Second Circuit, the government's goals of preserving the integrity of the drug approval process and reducing patient exposure to unsafe and ineffective drugs are not directly advanced by prohibiting manufacturers from discussing alternative uses with healthcare professionals, because other individuals and entities may communicate the same information, and such prescribing by physicians continues to be lawful.<sup>70</sup>

Moreover, even if FDA's restrictions on manufacturer speech about approved uses and medically accepted alternative uses of FDA-approved medicines directly furthers a government interest such as reducing patient exposure to unsafe or ineffective medicines, the prohibitions would likely still fail under the *Central Hudson* test, because FDA could use a more narrowly tailored means to achieve these goals. In *Thompson v. Western States Medical Center*, the Court noted that "if the Government could achieve

<sup>65</sup> Hall, *supra* note 46, at 11.

<sup>66</sup> Carver, *supra* note 52, at 171.

<sup>67</sup> *Id.* at 173.

<sup>68</sup> *Id.* at 183–84 (citing Wash. Legal Found. v. Friedman, 13 F. Supp. 2d 51, 69–71 (D.D.C. 1998)).

<sup>69</sup> *Sorrell v. IMS Health Inc.*, 131 S. Ct. 2653, 2658 (2011) (citations omitted). This is a long-standing principle. See *Va. State Bd. of Pharmacy v. Va. Citizens Consumer Council*, 425 U.S. 748, 773 (1976); *Washington Legal Foundation v. Friedman*, 13 F. Supp. 2d 51, 69–71 (D.D.C. 1998).

<sup>70</sup> *United States v. Caronia*, 703 F.3d 149, 166–67 (2d Cir. 2012).

its interests in a manner that does not restrict speech, or that restricts less speech, the Government *must* do so.”<sup>71</sup> There are many less restrictive alternatives available to the government other than completely prohibiting certain speech by manufacturers, such as developing a “warning or disclaimer system.”<sup>72</sup>

### III. PATIENT AND PROVIDER GROUPS SPEAK OUT: FDA SHOULD AMEND ITS CURRENT APPROACH TO HELP ENSURE THAT HEALTHCARE PROFESSIONALS RECEIVE CURRENT AND ACCURATE INFORMATION ABOUT THE MEDICINES THEY PRESCRIBE FOR PATIENTS

As patients, we all expect our healthcare professionals to be well informed about the medicines that they prescribe. Recently, patient and provider groups have participated in dialogs about the need to ensure that FDA’s interpretations of the FDCA and respective regulations keep pace with medical innovation.<sup>73</sup> In April 2014, the House Energy & Commerce Committee announced the launch of the 21st Century Cures Initiative, an attempt by Congress to find new ways to help accelerate the discovery, development, and delivery of new medicines and treatment options for patients.<sup>74</sup> Numerous stakeholders have submitted white papers in response to this initiative providing recommendations on how to improve the quality of patient care in the United States.

Some patient groups, such as the Society for Women’s Health Research (SWHR) and the National Organization for Rare Disorders (NORD), emphasized the importance for “open and transparent communication of important scientifically accurate data” and discussed how FDA’s current regulatory framework prohibits companies from sharing much of the accurate, data-driven information that they collect about approved products.<sup>75</sup> Furthermore, some healthcare professionals also expressed concern that FDA’s current restrictions on the speech of manufacturers may limit their ability to be well informed about the medicines they prescribe.<sup>76</sup>

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<sup>71</sup> 535 U.S. 357, 371 (2002) (emphasis added).

<sup>72</sup> *Caronia*, 703 F.3d at 168 (citing 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, 334 (2011)).

<sup>73</sup> See, e.g., Letter from Nolan, *supra* note 10.

<sup>74</sup> ENERGY & COMMERCE COMM., U.S. HOUSE OF REPRESENTATIVES, 21ST CENTURY CURES: A CALL TO ACTION (2014), available at <http://energycommerce.house.gov/sites/republicans.energycommerce.house.gov/files/analysis/21stCenturyCures/20140501WhitePaper.pdf>; see also *List of “A Call to Action” White Paper Respondents*, ENERGY & COM. COMMITTEE, <http://energycommerce.house.gov/sites/republicans.energycommerce.house.gov/files/analysis/21stCenturyCures/20140813CallToActionRespondents.pdf> (last visited Feb. 15, 2015).

<sup>75</sup> Letter from Nolan, *supra* note 10 (“Access to company data should be established in a way that provides for appropriate communication to health care professionals and patients on medication usage that could improve patients’ health outcomes.”); Letter from Peter L. Saltonstall, President & CEO, Nat’l Org. for Rare Disorders to Honorable Fred Upton, Chairman, Comm. on Energy & Commerce, on 21st Century Cures (May 30, 2014) (on file with author) (“[T]he government severely restricts what drug companies can say about new research and about off-label uses, thus cutting off information from the most knowledgeable sources.”).

<sup>76</sup> *Barriers in Health Communication: Hearing Before the H. Energy and Commerce Subcomm. on Health*, 113th Cong. (2014) (statement of Gregory F. Schimizzi, Cofounder, Coalition of State Rheumatology Organizations) (“By limiting the sharing of information [about approved and medically accepted alternative uses of FDA-approved medicines by pharmaceutical companies], physicians are hampered in their ability to access all available sound medical evidence and firm scientific rationale necessary to treat patients with difficult problems.”).

In addition to participating in the 21st Century Cures Initiative, some patient groups and healthcare professionals responded negatively to the aforementioned revised draft guidance entitled “Distributing Scientific and Medical Publications on Unapproved New Uses.”<sup>77</sup> For example, the Alliance of Specialty Medicine submitted a letter to FDA expressing its concern that the revised approach “inappropriately restricts specialty physicians’ access to scientific information provided by manufacturers on safe and effective use of medical products.”<sup>78</sup> The Alliance noted that “[t]o enhance patient care, physicians must have unrestricted access to truthful, non-misleading information about the benefits and risks of all therapies available for treatment, including medically accepted alternative uses of approved prescription drugs, biologics, and/or devices.”<sup>79</sup> Similarly, in response to the proposed changes to the draft guidance removing the favorable language for alternative uses of medications, the Ovarian Cancer National Alliance submitted a letter “urg[ing] FDA to reconsider some of its proposed language changes, which could potentially chill off-label use of oncology drugs and the dissemination of scientific information about non-approved uses.”<sup>80</sup>

In short, there appears to be a convergence in policy arenas and in the courts: FDA’s restrictions on companies’ ability to share truthful, non-misleading information about information about medicines that may appear outside of the approved labeling can harm patient care and run askew of the First Amendment.

#### IV. ENVISIONING A NEW PARADIGM: KEY PRINCIPLES FOR A NEW REGULATORY FRAMEWORK

Given recent developments in First Amendment jurisprudence and growing discussions among providers, patients, and lawmakers about the need for manufacturers to share accurate, data-driven scientific information about medicines, FDA should modify its existing regulatory framework to enable manufacturers to share more freely truthful and non-misleading information about both approved uses and also medically accepted alternative uses of FDA-approved medicines. For example, FDA should allow manufacturers to share information with healthcare professionals including observational data and real world evidence based on actual patient records, retrospective analyses, references to sub-population data and other endpoints, claims supported by less than two-well controlled studies, pharmacoeconomic information that can inform patient treatment decisions. Statements containing such information should be truthful, non-misleading and accompanied by sufficient information to establish context for medically sophisticated audiences (e.g., healthcare professionals, health plans, and Pharmacy Benefit Management Services). As described above, much of this information would not satisfy FDA’s current construction of the “substantial evidence” test, even though such data or analyses could help nurses and physicians improve patient care when communicated appropriately.

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<sup>77</sup> FOOD & DRUG ADMIN., REVISED DRAFT GUIDANCE FOR INDUSTRY: DISTRIBUTING SCIENTIFIC AND MEDICAL PUBLICATIONS ON UNAPPROVED NEW USES—RECOMMENDED PRACTICES (2014), available at <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm387652.pdf>.

<sup>78</sup> Letter from the Alliance of Specialty Med., to Leslie Kux, Assistant Comm’r for Policy, Food & Drug Admin. (May 2, 2014), available at [http://www.specialtydocs.org/files/Alliance\\_FDA\\_Letter\\_5.2.14.pdf](http://www.specialtydocs.org/files/Alliance_FDA_Letter_5.2.14.pdf).

<sup>79</sup> *Id.*

<sup>80</sup> Letter from Calaneet Balas, CEO, Ovarian Cancer Nat’l Alliance, to Bryant Godfrey, Senior Lead Regulatory Counsel, Ctr. for Drug Evaluation & Research, Food & Drug Admin., on Docket No. FDA-2008-D-0053 (May 1, 2014), available at <http://www.ovariancancer.org/wp-content/uploads/OCNA-Comments-FDA-2008-D-0053-0132.pdf>.

Carefully constructed safe harbors and revised regulations, guidance documents, and policies would enhance public health and preserve the integrity of the drug approval process rather than threaten either of these governmental interests. A regulatory framework that is consistent with First Amendment principles and protects the public health should adhere to five key principles.<sup>81</sup> These principles are discussed below.

1. *All Communications About Medicines Should Be Truthful and Non-Misleading:* Consistent with the First Amendment and public health, all communications about medicines (including those of companies, payers, and the government) should be truthful and non-misleading in order to benefit patient care. Regulators should not discriminate based on the identity of the speaker or the content of the message. FDA therefore should not enforce a double standard in which it censors information shared by manufacturers that the government would provide itself. All materials about medicines should be factually correct and should contain material benefit and risk information necessary for trained professionals to make informed treatment decisions. To achieve this goal, FDA should provide a clear definition of the term “false or misleading speech” and require regulated labeling to be accompanied by sufficient information to establish context for medically sophisticated audience.<sup>82</sup> Furthermore, FDA should explicitly state, consistent with *Sorrell*,<sup>83</sup> that speech will be considered misleading only if a reasonable person with the special knowledge or skills of the individual to whom the speech was directed would consider the speech misleading.<sup>84</sup>
2. *Balance Patient Benefit and Potential Risk to Determine Appropriate Limitations on Healthcare Communications by Biopharmaceutical Companies:* In order to enhance patient care, healthcare professionals deserve access to accurate information about the benefits and risks of all medicines available for treatment. Any limitations on healthcare communications should be proportional to the patient risk based on factors including the approval status of the medicine, general medical acceptance of the treatment (e.g., appearance in compendia and/or clinical practice guidelines), and the level of scientific sophistication of the audience. Therefore, we propose that healthcare professionals, especially those sophisticated groups making formulary or coverage decisions, deserve access—without having to ask for it—to much more robust information than is typically contained in the approved labeling

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<sup>81</sup> A central feature of this modified framework is that it should only govern the discussions between biopharmaceutical companies and healthcare professionals, scientists, payers, and formulary committees—not communications with patients or other healthcare consumers—since sophisticated audiences have the training and experience to interpret and analyze information from a variety of different sources.

<sup>82</sup> FDA could use the “true statement” and “fair balance” regulations for prescription drug advertisements as a foundation for the definition of “false and misleading” in this context. See 21 C.F.R. § 202.1(e) (2014).

<sup>83</sup> *Sorrell v. IMS Health Inc.*, 131 S. Ct. 2653, 2670–71 (2011).

<sup>84</sup> Using a sophisticated audience standard is typical under the Lanham Act, consumer protection law, and tort law. See WILLIAM L. PROSSER, *LAW OF TORTS* § 32, at 161–66 (4th ed. 1971); see e.g., *U.S. Healthcare Inc. v. Blue Cross of Greater Philadelphia*, 898 F.2d 914, 922 (3d Cir. 1990); *Utah Medical Products, Inc. v. Clinical Innovations Associates, Inc.*, 79 F. Supp. 2d 1290, 1309 (D. Utah 1999), *aff'd*, 251 F.3d 171 (Fed. Cir. 2000); *Plough, Inc. v. Johnson & Johnson Baby Products Co.*, 532 F. Supp. 714, 717 (D. Del. 1982). Similarly, to determine whether promotional claims are deceptive, the Federal Trade Commission (FTC) examines the effect of the representations or sales practices on the target audience. “[A] practice or representation directed to a well-educated group, such as a prescription drug advertisement to doctors, would be judged in light of the knowledge and sophistication of that group.” *FTC Policy Statement on Deception*, FED. TRADE COMMISSION, <http://www.ftc.gov/public-statements/1983/10/ftc-policy-statement-deception> (last visited Feb. 15, 2015) (policy statement dated Oct. 14, 1983).

for both approved medicines for approved uses, as well as alternative uses that are routinely prescribed, reimbursed, and contained in government recognized compendia and physician practice guides. Here, there is real risk for patients, if their healthcare professionals are *denied* full access to information from manufacturers.<sup>85</sup>

3. *Permit Manufacturers to Use Robust Disclosures/Disclaimers to Disclose Limitations of Data Rather Than Prohibit Certain Healthcare Communications:* As the courts have noted, including adequate disclosures regarding risks and the limitations of scientific understanding are preferable (and most likely a required less restrictive alternative) to prohibiting certain healthcare communications. Such disclosures could help ensure that medical communications are data-driven and transparent. For example, FDA could revise its interpretation of the “substantial evidence” requirement; instead of requiring that any information disseminated by a manufacturer generally be supported by at least two adequate and well-controlled clinical trials, FDA could allow a manufacturer to meet the “substantial evidence” requirement for labeling in other instances if the information sharer provides robust disclosures that give sophisticated listeners the ability to analyze and interpret the information and prevent the speech from being misleading.
4. *Provide Incentives for Sponsors to Continue to Seek Supplemental Indications for Approved Medicines:* FDA should incorporate additional incentives for sponsors to continue to seek supplemental indications for approved medicines in a modified regulatory framework. For example, FDA should consider how it might streamline the process for sponsors to obtain additional labeled indications by allowing the use of real world evidence data in supplemental new drug applications rather than requiring a full battery of time-intensive randomized clinical trials for drugs that are already FDA-approved and being prescribed for a wide range of patients.<sup>86</sup>
5. *Allow Companies to Provide Adequate Directions for Use for Both Approved and Medically Accepted Alternative Uses of FDA-Approved Medicines:*

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<sup>85</sup> In this Article, we distinguish between *medically-accepted* alternative uses and *non-medically accepted* investigational uses of approved medicines or investigational medicines. Under the *Central Hudson* balancing analysis, the patient and physician’s interest in having additional truthful, non-misleading information about medicines that are being widely prescribed for approved and medically accepted alternative uses significantly outweighs any potential regulatory interests that FDA might have to restrict the dissemination of such information. It is conceivable that the *Central Hudson* balance may shift with respect to speech about non-medically accepted uses of approved drugs or uses about investigational (unapproved) drugs. This is so because: (1) far fewer patients would likely be receiving prescriptions for such uses, and thus the patient and physician interests in receiving more information about those uses is diminished; and (2) not only are such drugs and/or uses not FDA-approved, but also the efficacy and safety of those uses and/or those medicines have not yet been recognized by the medical community, and thus potential risks to patients could be higher. Of course, there is still strong First Amendment protection for “scientific exchange” about investigational drugs or investigational uses, and FDA’s current regulations reflect this. 21 C.F.R. § 312.7(a) (2014); *see also* Washington Legal Foundation v. Friedman, 13 F. Supp. 2d 51, 62 (D.D.C. 1998) *appeal dismissed, judgment vacated in part sub nom.* Washington Legal Found. v. Henney, 202 F.3d 331 (D.C. Cir. 2000); Bracco Diagnostics, Inc. v. Amersham Health, Inc., 627 F. Supp. 2d 384, 456–58 (D.N.J. 2009) (holding that a scientific article published in the New England Journal of Medicine is speech protected by the First Amendment).

<sup>86</sup> *See, e.g.*, DELOITTE, DELOITTE’S PATH TO 21ST CENTURY CURES—A CALL TO ACTION 13 (2014), available at <http://energycommerce.house.gov/sites/republicans.energycommerce.house.gov/files/analysis/21stCenturyCures/CallToActionResponses63-65.pdf> (noting “[t]he goal of the innovations in statistical methods coupled with new sources of data is to enable a more efficient process for developing products and opportunities to develop products for rare conditions that do not lend themselves to the [randomized clinical trial] model because of feasibility constraints.”).

Companies must be able to provide adequate directions for use of both approved and medically accepted alternative uses of FDA-approved medicines for patients. Therefore, a modified regulatory framework should comply with First Amendment principles and amend FDA's overly broad and circular interpretation of the requirement that a prescription drug label must bear adequate direction for its intended use. For example, FDA could identify certain categories of speech that are considered to be truthful and non-misleading if accompanied by sufficient disclosures (e.g. speech about FDA approved uses and speech about medically accepted alternative uses) and exempt speech in these categories from serving as the basis for a misbranding charge under the FDCA.<sup>87</sup>

In addition to using these five principles as a guide when reforming the existing regulatory framework, FDA should adopt a regulatory definition of "labeling" that comports with the FDCA and the First Amendment. Specifically, FDA should amend its current interpretation of the term "labeling," so that it pertains only to communications that are appropriately identified as labeling rather than all communications by a manufacturer.<sup>88</sup> FDA's current interpretation of the term is far too expansive and essentially reads both the written requirement and the "accompanying such [drug]" proximity requirement out of the Act.<sup>89</sup> Instead, FDA should carefully consider the purpose served by materials that are distributed before determining that they constitute labeling. For example, FDA should establish that non-physical and oral communications are not "labeling." This interpretation of "labeling" would conform to the definition of labeling in the FDCA and relevant case law.<sup>90</sup>

## CONCLUSION

FDA plays a critical role in ensuring that patients and physicians have confidence that prescribed medicines are safe and effective for their approved uses. Yet, modern medicine demands an ever increasing information flow. It is no longer appropriate for

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<sup>87</sup> For communications pertaining to medically accepted alternative uses of FDA-approved medicines, perhaps the most prominent disclosure could be that the use for which the information pertains is not an FDA-approved use. A reformed FDA regulatory regime could provide for such other disclosures and qualifiers that may be necessary to ensure that communication about information outside of FDA labeling is not misleading.

<sup>88</sup> As previously discussed, FDA's expansive interpretation of labeling significantly chills a manufacturer's First Amendment protected speech, because any truthful and non-misleading communication about unapproved uses of medicines violates criminal prohibitions against the introduction of new drugs and misbranded drugs into interstate commerce if the speech appears in the drug's labeling.

<sup>89</sup> See Krista Hessler Carver, *A Global View of the First Amendment Constraints on FDA*, 63 *FOOD & DRUG L.J.* 151, 189 (2008).

<sup>90</sup> The FDCA defines labeling as "all labels and other written, printed, or graphic matter (1) upon any article or any of its containers or wrappers, or (2) accompanying such article." 21 U.S.C. § 321(m) (2012). Courts have held that the phrase "accompanying such article" can include certain materials that were not shipped in the same package as the drug. *Kordel v. United States*, 335 U.S. 345, 349 (1948). Most courts, however, have determined that materials only should be considered to be "labeling" if they are designed for use in the distribution and sale of the product, and can be considered part of an "integrated distribution program." For example, in *Kordel* the Court said "[i]n this case the drugs and the literature had a common origin and a common destination. The literature was used in the sale of the drugs. It explained their uses. Nowhere else was the purchaser advised how to use them. It constituted an essential supplement to the label attached to the package. Thus the products and the literature were interdependent . . ." *Id.* at 348 (emphases added); see also *Request for Comment on First Amendment Issues Before the U.S. Food & Drug Admin.* Docket No. 02N-0209, Comments of Pfizer Inc., at 73 (Sept. 13, 2002).

the practice of medicine and information exchange to be based solely on the contents of FDA-approved labeling as re-printed in the Physician's Desk Reference.

Both the advances of 21st century medicine, as well as courts' interpretation of the First Amendment's guarantee of free expression, point in one direction: sharing more information rather than less. It is critical that FDA interpret the FDCA in a way that creates a clear, meaningful safe harbor for manufacturers to share with healthcare professionals a much greater amount of truthful, non-misleading information about both approved uses and medically accepted alternative uses of FDA-approved medicines. Without such a safe harbor, FDA's current interpretation of the FDCA is highly vulnerable to a First Amendment challenge, primarily due to (i) FDA's overbroad restrictions on companies' communications and (ii) the Agency's imposition of speaker-based and content-based distinctions. Enabling manufacturers to share accurate, data driven information about complex, modern medicines will enhance patient outcomes. More robust information sharing, particularly with respect to approved and medically accepted alternative uses of FDA-approved medicines, combined with transparent qualifications and disclaimers, will help ensure that healthcare professionals may access the most comprehensive and timely information and data about these treatments from the companies that arguably know more about their medicines than anyone else.<sup>91</sup>

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<sup>91</sup> See Regulatory Information: "Off-Label" and Investigational Use of Marketed Drugs, Biologics, and Medical Devices—Information Sheet, FOOD & DRUG ADMIN., <http://www.fda.gov/regulatoryinformation/guidances/ucm126486.htm> (last updated June 25, 2014); see also Coleen Klasmeier & Martin H. Redish, *Off-Label Prescription Advertising, The FDA, and The First Amendment: A Study in the Values of Commercial Speech Protection*, 37 AM. J.L. & MED. 315 (2011).