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April 19, 2017

Division of Dockets Management
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, MD 20852

COMMENTS ON
MANUFACTURER COMMUNICATIONS REGARDING UNAPPROVED USES OF APPROVED OR CLEARED MEDICAL PRODUCTS
Docket No. FDA-2016-N-1149

Public Citizen, a consumer organization with members and supporters nationwide, submits these comments in response to the request for comment on "Manufacturer Communications Regarding Unapproved Uses of Approved or Cleared Medical Products," published in the Federal Register by the Food and Drug Administration (FDA) on September 1, 2016. Primarily through its Health Research Group, Public Citizen has long been an advocate for strong regulation of drugs and medical devices for the protection of patients. Public Citizen appreciates the agency's attention to this important public health issue and the opportunity to provide these comments.

At least since the 1990s, pharmaceutical and medical device companies have been pushing back against FDA restrictions on marketing drugs and medical devices for uses not approved by the agency. After only limited initial success, the industry recently stepped up its efforts to roll back these restrictions. At its heart, the industry push challenges two central tenets of the FDA regulatory scheme: (1) objective scientific evaluation of evidence concerning each proposed use of a drug or device is needed to protect consumers and (2) selling drugs and devices for therapeutic uses in the absence of validation by such evaluation is false or misleading. The development of appropriate policy in this area requires an understanding of the development of the FDA's regulatory authority. Accordingly, we begin with a short historical summary. We then discuss the risks to patients when manufacturers promote their products for unapproved uses and the unreliability of journal articles as a basis for physicians' decisionmaking. Finally, we explain that the First Amendment does not support the industry call for relaxation of the restrictions on promoting products for uses that the FDA has not approved as safe and effective for patients.

BACKGROUND, FDA'S RESPONSIBILITY, AND SUBSTANTIAL GOVERNMENT INTERESTS

The current regulatory regimes for drugs and medical devices developed in response to real-world situations that highlighted the need for an objective decisionmaker to assess the safety

and effectiveness of a drug or device before it is sold to patients. Congress took the first step in 1906, passing the Pure Food and Drugs Act, partially in response to cure-all claims for worthless and dangerous medicines.[1] The law prohibited the sale of misbranded or adulterated drugs but required no premarketing review and no prior testing or showing of safety. And to force a drug off the market, the government bore the burden of proving that the product's labeling was false and misleading.[2]

Then, in 1937, 105 people died from taking Elixir Sulfanilamide, a liquid form of the first sulfa antibiotic. The elixir was marketed without toxicity testing of the ingredients, which included the toxic chemical diethylene glycol.[3] This incident prompted passage of the 1938 Food, Drug, and Cosmetic Act (FDCA), which required manufacturers to submit premarket notifications demonstrating the safety of each new drug before marketing. Specifically, the law required the manufacturer of a "new drug"—that is, a drug "not generally recognized, among experts … as safe and effective for use"—to submit to the FDA, in advance of marketing a new product, a "new drug application" (NDA) demonstrating "adequate testing" showing that the drug is safe for "use under the conditions prescribed" in its labeling.[4] The law thus prohibited, for the first time, marketing a new drug for any use not approved by the FDA.

A near miss in 1960 prompted another important improvement in drug regulation. The FDA considered but ultimately refused to approve thalidomide. The drug was marketed in Europe and elsewhere for insomnia and morning sickness in pregnant women, and subsequently was found to cause severe human birth defects.[5] The tragedy sparked congressional hearings, which revealed that drug companies were making effectiveness claims that were unsupported or based on shoddy scientific evidence.[6] In 1962, Congress responded by strengthening the drug approval process to require not only proof of safety, but also "substantial evidence" of effectiveness for a drug's intended use.[7] This evidence must be supported by "adequate and well-controlled investigations."[8] Moreover, because a drug may be safe and effective for one use but unsafe or ineffective for another, the law requires a manufacturer of a drug that has already been approved through an NDA to submit a supplemental NDA demonstrating the drug's safety and effectiveness for any additional use before labeling or marketing the drug for that new use.[9] The

[1] Janssen W. Outline of the History of U.S. Drug Regulation & Labeling. *Food Drug Cosm. L.J*. 1981;36:420, 422.
[2] 21 U.S.C. § 352(a); Richard A. Merrill, *The Architecture of Gov't Regulation of Med. Prods.*, 82 Va. L. Rev. 1753, 1761 (1996).
[3] Wax P. Elixirs, diluents, and the passage of the 1938 Federal Food, Drug and Cosmetic Act. *Ann Intern Med*. 1995;122:456–461.
[4] 21 U.S.C. §§ 321(p), 355(a), (b), (d).
[5] Avorn J. Learning about the safety of drugs—a half-century of evolution. *New Engl J Med*. 2011:365:2151–2153.
[6] FDA. Promoting Safe and Effective Drugs for 100 Years. Available at http://www.fda.gov/AboutFDA/WhatWeDo/History/CentennialofFDA/CentennialEditionofFDAConsumer/ucm093787.htm.
[7] 21 U.S.C. §§ 321(p), 355(a), (b), (d).
[8] *Id*. § 355(d).
[9] *See* 21 C.F.R. § 314.70.

requirement of adequate and well-controlled studies was "revolutionary" and invaluable in advancing pharmaceutical safety and effectiveness.[10]

The 1938 and 1962 laws protect patients by mandating a review process that enables the FDA to detect unsafe or ineffective medicines *before* they reach consumers and cause harm. The resulting premarket approval process is a cornerstone of modern drug safety regulation, serving the separate but complementary goals of protecting the public from dangerous drugs and preventing false and misleading claims.[11] Indeed, "[t]here are few, if any, more important functions performed by any regulatory agency than … ensuring that when a citizen takes a prescription drug, that individual has absolute assurance that the product is safe and effective for the condition for which his physician has prescribed it."[12] The premarket review process is a crucial bulwark against the sorts of pseudo-scientific claims that characterized fraudulent medicine before federal regulation.

As the FDA recognizes, existing restrictions on manufacturer communications regarding unapproved uses of approved or cleared medical products are overwhelmingly justified by "substantial government interests related to health and safety," including, in particular, the following:

- motivating the development of robust scientific data on safety and effectiveness for each new use of a medical product;
- maintaining the premarket review process for safety and effectiveness of each intended use in order to prevent harm; protect against fraud, misrepresentation, and bias; and prevent the diversion of health care resources to ineffective treatments;
- ensuring required product labeling is accurate and informative;
- protecting the integrity and reliability of promotional information regarding medical product uses;
- protecting human subjects who are receiving experimental treatments, ensuring informed consent, and maintaining incentives for clinical trial participation;
- protecting innovation incentives, including statutory grants of exclusivity; and
- promoting the development of products for underserved patients.[13]

[10] Promoting safe and effective drugs for 100 years. FDA Consumer Magazine. Jan–Feb 2006. Available at www.fda.gov/AboutFDA/WhatWeDo/History/CentennialofFDA/CentennialEditionofFDAConsumer/ucm093787.htm. [Last accessed Mar. 9, 2017]

[11] *See Abigail Alliance for Better Access to Dev'l Drugs v. von Eschenbach*, 495 F.3d 695, 703 (D.C. Cir. 2007) (en banc).

[12] *See Wash. Legal Found. v. Friedman*, 13 F. Supp. 2d 51, 69 (D.D.C. 1998), *vacated on other grounds*, *Wash. Legal Found. v. Henney*, 202 F.3d 331 (D.C. Cir. 2000).

[13] FDA. Memorandum: Public health interests and first amendment considerations related to manufacturer communications regarding unapproved uses of approved or cleared medical products. Jan 2017. Available at https://www.regulations.gov/contentStreamer?documentId=FDA-2016-N-1149-0040&attachmentNumber=1&contentType=pdf. [Last accessed Feb. 28, 2017] at 3-16.

Together, these interests support the FDA's overarching mission of protecting and promoting public health. That interest outweighs any purported public health benefit of allowing manufacturer communications regarding unapproved uses of medical products.

DANGERS OF PROMOTION FOR UNAPPROVED USES

Although the FDA today approves new drugs and some medical devices before they are marketed, it—and the public—maintains a strong interest in evaluating the products' safety and effectiveness for any additional uses that were not evaluated at the time of initial approval. For example, a drug that poses a serious risk to the patient's immune system may merit approval to treat cancer but not to treat a headache. Thus, the FDA does not evaluate safety in a vacuum: For each proposed use, the agency balances the drug's risk of harm against its potential for benefit. Furthermore, the FDA has a powerful interest in ensuring that a drug is not only safe for each use for which a manufacturer markets it, but also effective. Marketing for a safe but ineffective use can have detrimental health effects if it diverts patients from effective treatment.[14]

Moreover, a drug's safety for a second use is not established once a drug has been approved (and thus deemed safe and effective) for a first use. To the contrary, a drug that is safe for one use can be life threatening for another. For example, the drug bromocriptine is safe for use in treating certain diseases, such as Parkinson's disease, but has been linked to strokes when used to suppress lactation in postpartum women. See 59 Fed. Reg. 43347 (1994) (FDA notice of withdrawal of approval for use to suppress lactation); FDA, http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/017962s065s068lbl.pdf, at 4, 11 (current product labeling, listing approved uses and warning against use by lactating women).

Accordingly, it is not surprising that harms associated with taking marketed drugs for unapproved uses have been well-documented. For example, starting in the mid-1980s, doctors increasingly prescribed estrogen–progestin hormone replacement drugs to postmenopausal women as a preventative measure against a range of illnesses, including heart disease, breast cancer, and Alzheimer's disease—uses that were not FDA-approved. After tens of millions of prescriptions had been written, a large, U.S. government-funded randomized clinical trial found that such unapproved uses of the drugs significantly increased risks of coronary heart disease, stroke, pulmonary embolism, and invasive breast cancer, and that these risks exceeded the drugs' benefits when prescribed for several off-label uses.[15]

Unfortunately, this example is just one of many.[16] Risperdal, Xyrem, Avandia, Zofran, and Neurontin are other well-known examples of drugs that caused significant injury as a result

[14] *See Friedman*, 13 F. Supp. 2d at 56–57 (noting evidence that off-label use of calcium channel blockers deprived patients of more effective treatments).

[15] Fletcher SW, Colditz GA. Failure of estrogen plus progestin therapy for prevention. *JAMA*. 2002;288:366-368; Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: Principal results from the Women's Health Initiative randomized controlled trial. *JAMA*. 2002;288:321-333.

[16] *See also, e.g.*, *Perry v. Novartis Pharm. Corp*., 456 F. Supp. 2d 678 (E.D. Pa. 2006) (Elidel approved as safe and effective to treat dermatitis, but poses risk of causing cancer when used off-label in patients less than two years old);

of the manufacturers' off-label promotion and marketing. And the problem is not limited to drugs, as demonstrated by the hundreds of patients seriously injured by unapproved uses of Medtronic, Inc.'s Infuse medical device.[17]

Although prescribing drugs and devices for unapproved uses is common, scientific evidence supporting most such uses is lacking. For example, an observational study published in 2008 examined the frequency with which drugs were prescribed for unapproved uses in the U.S. from January 2005 to June 2007.[18] The researchers found that, for the 25 drugs prescribed most frequently for unapproved uses that have inadequate evidence of effectiveness, 29 percent of the total prescriptions were for unapproved uses. Collectively, for these 25 drugs, scientific evidence was inadequate to support the effectiveness of the drugs for 82 percent of their off-label uses.

A more recent observational study conducted in Canada likewise found that the vast majority of off-label uses—81 percent—lacked strong scientific evidence of effectiveness.[19] Patients who received a prescription for an off-label use lacking strong evidence of effectiveness were 54 percent more likely to experience an adverse drug reaction that resulted in stopping use of the drug than those who were prescribed a drug for an approved use.

The increased risk of serious adverse events when drugs are prescribed for off-label uses, combined with the lack of strong evidence of benefit, demonstrates that a favorable risk–benefit relationship has not been established for most off-label uses of drugs and further supports strong restrictions against promotion of unapproved uses.

In addition, allowing broad promotion of drugs for unapproved uses would deter clinical trials of unapproved uses. Manufacturers would not invest in expensive testing of new uses if they were free to market their products for those uses without evidence of benefit. As a result, physicians, patients, and the FDA would be deprived of important information about safety and effectiveness.

Friedman, 13 F. Supp. 2d at 56–57 (noting off-label prescriptions of anti-arrythmic drugs encainide and flecainide to treat minor heart-rhythm disturbances in patients with recent heart attacks caused an estimated 3,000 to 10,000 patient deaths per year); *see generally* Henry A. Waxman, *A History of Adverse Drug Experiences: Congress Had Ample Evidence to Support Restrictions on the Promotion of Prescription Drugs*, 58 Food & Drug L.J. 299, 301–06 (2003) (detailing history of harms resulting from marketing of drugs for uses for which they had not been shown to be safe and effective).

[17] *See Patients who received Medtronic's Infuse product to get $8.45 million in settlements*, StarTribune, Aug. 2, 2016 ("Claims of injuries from such 'off-label' use have plagued Infuse almost from the time of its introduction into the market in 2002."); *Medtronic Says Device for Spine Faces Probe*; Wall St. J., Nov. 19. 2008 (describing Department of Justice probe into Medtronic's off-label promotion).

[18] Walton SM, Schumock GT, Lee KV, et al. Prioritizing future research on off-label prescribing: Results of a quantitative evaluation. *Pharmacotherapy*. 2008;28(12):1443-1452.

[19] Eguale T, Buckeridge DL, Verma A, et al. Association of off-label drug use and adverse drug events in an adult population. *JAMA Intern Med*. 2016;176(1):55-63.

MARKETING TECHNIQUES EXACERBATE THE RISKS

In its January 2009 guidance for industry on good reprint practices[20] and its more expansive February 2014 draft guidance on distributing scientific and medical publications on unapproved new uses,[21] the FDA articulated "safe harbor" policies that permit pharmaceutical and medical device manufacturers to disseminate scientific and medical journal articles and other materials describing unapproved uses of approved or cleared medical products, provided certain conditions are met. These guidelines allow drug companies to engage in public discourse and scientific debate, while addressing (although not wholly solving) the most common problems resulting from unregulated marketing of drugs for unapproved uses. For example, the guidelines attempt to address the problem of incomplete, skewed, or biased data by stating that reprints should be accompanied by a disclosure that identifies any conflicts of interest and by limiting a manufacturer's distribution of publications funded by, written at the request of, or influenced by the manufacturer. They also include additional provisions designed to ensure that distributed information is scientifically sound, stating, for example, that reprints should address well-controlled studies and be published in a generally available, peer-reviewed journal.[22]

Nonetheless, the FDA's policy of allowing distribution of peer-reviewed journal articles about unapproved uses allows companies to market drugs based on unreliable and in some cases deceptive evidence of safety and effectiveness. The FDA guidelines state that, if manufacturers distribute articles or other information as set forth in the guidance, the FDA does not intend to use such distribution as evidence of the manufacturer's "intent that the product be used for an unapproved new use" in violation of the FDCA. Yet the agency cannot overlook that the primary reason drug and device company representatives distribute scientific and medical information regarding unapproved uses undoubtedly is to promote those uses to physicians and other health care providers in the hope of increasing prescribing of the companies' products. Legalized off-label marketing—even under the safe-harbor conditions specified in FDA guidance—threatens the U.S. regulatory process for ensuring that prescription drugs and medical devices are safe and effective for their intended uses.

Peer-reviewed scientific and medical journals vary significantly in their credibility and rigor. But even among the most respected journals, the peer-review process suffers from shortcomings that can permit fraudulent or otherwise misleading articles to find their way into publication and then, via drug salespeople, into doctors' hands. Unlike the rigorous FDA review process for drugs and high-risk medical devices, the peer-review process for scientific and medical journals generally is not well equipped to uncover the wide range of problems that can undermine the integrity of clinical trial data, including outright fraud, flawed study design,

[20] FDA. 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: Guidance for industry. Jan 2009. Available at http://www.fda.gov/RegulatoryInformation/Guidances/ucm125126.htm. [Last accessed Mar. 9, 2017]
[21] FDA. Revised draft guidance for industry: Distributing scientific and medical publications on unapproved new uses—recommended practices. Feb 2014. Available at http://www.fda.gov/downloads/drugs/guidancecompliance regulatoryinformation/guidances/ucm387652.pdf. [Last accessed Mar. 9, 2017]
[22] *Id*.

failure to adhere to protocol-specified procedures, poorly conducted statistical analyses, and incomplete reporting of key data. Conflicts of interest resulting from financial relationships between authors of peer-reviewed journal articles and manufacturers can increase the likelihood of such problems. And most busy physicians and other health care providers are even less equipped than journal peer reviewers to assess the validity and reliability of data presented in journal articles that are distributed by manufacturers.

Underscoring the limitations of relying on peer-reviewed scientific and medical journals, the FDA recently explained:

> Although some of the assurances from independent review for a particular study can be obtained by review by non-governmental entities (such as peer review coordinated by a scientific or medical journal), the standards governing FDA review provide an assurance of data completeness, scientific rigor, and a thoroughness of evaluation that are not met by the more narrow examination of the peer review process, given the limited data typically available to and reviewed by peer reviewers, the more limited number of peer reviewers (and thus more limited areas of expertise), and the scope of a journal article.[23]

Relying on articles published in peer-reviewed journals without digging deeper into the underlying data—as occurs when FDA scientists review new drug applications, medical device premarket approval applications, and some 510(k) device premarket clearance applications—can lead to the rapid adoption of ineffective or unsafe unapproved uses of drugs and medical devices and, thus, put patients in harm's way.

Research Fraud and Misconduct — Research fraud and misconduct represent the most serious threat to the integrity of data presented in journal articles. The FDA itself has noted that fraud and misconduct have occurred in all phases of clinical research and have involved enrolling unqualified subjects, backdating information, fabricating data from tests that were not performed, failing to report adverse events, deviating from protocols, covering up mistakes, and submitting false data for publication.[24]

Evidence suggests that the incidence of detected research fraud and misconduct, although very low, has increased significantly. For example, a 2012 study of the PubMed database found that the percentage of scientific articles retracted due to fraud had increased approximately tenfold since 1975.[25] Fraud or suspected fraud were the most commonly identified reasons for retraction of an article, occurring in 43 percent of cases. The study authors noted that "the current number of articles retracted because of fraud represents an underestimation of the actual number of fraudulent articles in the literature."

[23] FDA Memorandum, *supra* note 13, at 9.
[24] Hamrell MR. Raising suspicions with the Food and Drug Administration: Detecting misconduct. *Sci Eng Ethics*. 2010;16(4):967-704.
[25] Fang FC, Steen RG, Casadevall A. Misconduct accounts for the majority of retracted scientific publications. *PNAS*. 2012;109(42):17028-17033. (Correction: *PNAS*. 2013;110(3):1137.)

Biased Study Design — Equally insidious and far more widespread than outright research fraud are a wide range of practices that result in clinical trial bias. In a 2015 editorial in the *Mayo Clinic Proceedings*, Prasad and Berger coined the term "hard-wire bias" to describe sources of potential bias originating in the initial design of randomized, double-blind clinical trials.[26] They pointed out that hard-wire bias cannot be corrected by using statistical methods or reanalysis. Examples described by the authors include selection bias and unequal-comparison bias.

Selection bias can occur when inclusion and exclusion criteria result in a very narrowly defined subject population, which prevents the generalizability of the results to a broader patient population, even though results of clinical trials routinely are used to justify use of a drug in a broader population.[27] Unequal-comparison bias stems from designs that disadvantage one trial group relative to another, such as selecting an active comparator for the control group that is not consistent with standard-of-care treatment.

Publication Bias — Another well-documented problem that adversely affects the scientific and medical literature is publication bias—the tendency of investigators to submit, and the tendency of editors and reviewers to accept, manuscripts with positive research findings. A 2009 systematic review by the Cochrane Library of studies assessing publication bias found that clinical trials with positive findings were nearly four times more likely to be published than trials with negative findings.[28] Furthermore, trials with positive findings tended to be published sooner—after four to five years—than those with negative findings, which were published after six to eight years.

Publishing Data from Phase 2 Clinical Trials Without Confirmatory Data from Phase 3 Trials — Under the FDA's existing guidance for industry on good reprint practices, pharmaceutical and medical device manufacturers may promote drugs and devices for unapproved uses by distributing reprints of medical journal articles that present results of phase 2 clinical trials that tested medical products for such uses even if phase 3 trials related to those uses have not been conducted or completed. As the agency is well aware, however, results of phase 2 clinical trials can provide misleading information about the safety and effectiveness of products.

The FDA highlighted this point in its recent report describing 22 carefully documented case studies of drugs, vaccines, and medical devices for which promising phase 2 clinical trial results were not confirmed in phase 3 trials.[29] The agency's analysis of these cases revealed that phase 3 results did not confirm effectiveness in 14 cases, did not confirm safety in one case, and failed to confirm both safety and effectiveness in seven cases.[30] Six cases involved prescription

[26] Prasad V, Berger V. Hard-wired bias: How even double-blind, randomized controlled trials can be skewed from the start. *Mayo Clin Proc*. 2015;90(9):1171-1175.
[27] *Id*.
[28] Hopewell S, Loudon K, Clarke MJ, et al. Publication bias in clinical trials due to statistical significance or direction of trial results. *Cochrane Database of Systematic Reviews.* 2009, Issue 1. Art. No.: MR000006. DOI:10.1002/14651858.MR000006.pub3.
[29] FDA. 22 Case Studies Where Phase 2 and Phase 3 Trials Had Divergent Results. Available at https://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Reports/UCM535780.pdf. [Last accessed Feb. 27, 2017] at 2.
[30] *See id*.

drugs that were already approved by the FDA for one use but undergoing clinical testing for another use.[31] The selected cases were "chosen from a large pool of similar examples."[32] The FDA noted the following:

> These unexpected results [from phase 3 trials] could occur even when the phase 2 study was relatively large and even when the phase 2 trials assessed clinical outcomes. In two cases, the phase 3 studies showed that the experimental product increased the frequency of the problem it was intended to prevent.[33]

The agency concluded the following:

> [T]he 22 cases explored in this paper demonstrate that phase 2 results can inaccurately predict safety and/or effectiveness for medical products in a wide range of diseases and patient populations. These cases also help illustrate the potential public health implications of undue reliance on phase 2 studies and the benefits of conducting Phase [3] studies. As a result of the Phase [3] studies discussed in this paper, patients outside of clinical trials were not subjected to drugs that would not benefit them or to the risk of unnecessary serious toxicities, and did not suffer unnecessary financial expenditures. Where effective alternative therapies existed, they were not diverted from proven treatments; where an implanted medical device was at issue, patients were spared unnecessary surgical procedures.[34]

The FDA's recent report thus demonstrates the risks of allowing promotion of uses before successful completion of phase 3 studies and subsequent review and approval by the FDA. Until that point, physicians and patients cannot be reasonably assured of the safety and effectiveness of the product.

Selective Reporting in Educational Materials and Published Articles — Allowing distribution of peer-reviewed literature about unapproved uses also skews physicians' perceptions of the safety and effectiveness of those uses because, as has been well documented, manufacturers selectively report study findings that are most favorable for their products. When selecting educational material to send to doctors or to present at seminars, manufacturers choose material that plays up positive results and omits information about side effects, adverse reactions, and warnings.[35,36] For example, studies comparing information in documents submitted to the FDA for approval of a drug[37,38] or high-risk medical device[39] with information reported in peer-

[31] *See id*. at 34.
[32] *Id*. at 2.
[33] *Id*.
[34] *Id*. at 29-30
[35] *Washington Legal Foundation v. Friedman*, 13 F. Supp. 2d 51 (D.D.C. 1998), *vacated on other grounds*, 202 F.3d 331 (D.C. Cir. 2000).
[36] Ford M. Another use of OxyContin: The case for enhancing liability for off-label drug marketing. *BU L Rev*. 2003;83:429-464.
[37] Rising K, Bacchetti P, Bero L. Reporting bias in drug trials submitted to the Food and Drug Administration: Review of publication and presentation. *PLoS Med*. 2008;5(11): e217. DOI:10.1371/journal.pmed.0050217. (Correction: *PLoS Med* 6(1): e1000017. doi:10.1371/journal.pmed.1000017)

reviewed medical journal articles have revealed frequent discrepancies in identified primary endpoints and primary study results. Likewise, another study found that drug companies selectively report the outcomes of clinical trials.[40] Unsurprisingly, the studies drug companies choose not to publish overwhelmingly report negative or inconclusive results.[41] In 2004, for example, Merck withdrew Vioxx from the market after revelations emerged that the company had suppressed evidence that the drug caused an increased risk of heart attack and that the company had attempted to discredit or "neutralize" doctors who were critical of the drug.[42]

The FDA itself, in its 2010 Transparency Task Force report, noted, "Selective publication of clinical trials results has, in the past, created a misleading picture of the safety and efficacy of a product, with negative implications for the public health. This is particularly pronounced when the product is used off-label."[43]

Ghostwriting — The problem of inherent bias in the reported studies is exacerbated when companies hire ghostwriters or recruit academics to pose as authors.[44] For example, Parke-Davis designed and commissioned research to promote its drug Neurontin and devised a "publication strategy" that included contracts with medical education companies to write articles on specified topics involving off-label use.[45]

In sum, restrictions on marketing drugs and devices for unapproved uses are crucial because reliance on publication of a study is no substitute for the FDA's rigorous, independent evaluation of the evidence. "FDA assigns review teams and primary reviewers who specialize in that scientific discipline to review that portion of the application and to generate a written evaluation. FDA then integrates the conclusions from these separate review activities to

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[38] Turner EH, Knoepflmacher D, Shapley L. Publication bias in antipsychotic trials: An analysis of efficacy comparing the published literature to the US Food and Drug Administration database. *PLoS Med*. 2012;9(3): e1001189. DOI:10.1371/journal.pmed.1001189.

[39] Chang L, Dhruva SS, Chu J, et al. Selective reporting in trials of high risk cardiovascular devices: Cross sectional comparison between premarket approval summaries and published reports. *BMJ*. 2015 June 10;350:h2613.

[40] Vedula SS, Bero L, Scherer RW, Dickersin K. Outcome Reporting in Industry-Sponsored Trials of Gabapentin for Off-Label Use. *New Engl J Med*. 2009;361:1963–1971.

[41] Turner EH, Matthews AM, Linardatos E, et al. Selective Publication of Antidepressant Trials and Its Influence on Apparent Efficacy. *New Engl J Med*. 2008;358:252–260.

[42] Walters C. Researchers Reveal Merck's Ghostwritten Vioxx Studies. Trial. July 2008.

[43] Food and Drug Administration Transparency Task Force. FDA Transparency Initiative: Draft Proposals for Public Comment Regarding Disclosure Policies of the U.S. Food and Drug Administration. May 2010. Available at http://www.fda.gov/downloads/AboutFDA/Transparency/PublicDisclosure/GlossaryofAcronymsandAbbreviations/UCM212110.pdf. [Last accessed Nov. 6, 2016]

[44] Ross J, Hill KP, Egilman DS, Krumholz HM. Guest Authorship and Ghostwriting in Publications Related to Rofecoxib. *JAMA*. 2008;1800–1812.

[45] *See* Landefeld S, Michael A, Steinman M. The Neurontin Legacy—Marketing through Misinformation and Manipulation. *New Engl J Med*. 2009;360:103–106 (Parke-Davis engaged in 'the systematic use of deception and misinformation to create a biased evidence base and manipulate physicians' beliefs and prescribing behaviors.").

determine the appropriate outcome for the application."[46] The agency is correct that its "multi-disciplinary scientific review cannot be replicated by individual health care providers."[47]

As Avorn and colleagues aptly explained in their 2015 *New England Journal of Medicine* article, "physicians and patients could not be expected to determine whether a given drug was safe and effective without having the benefit of the lengthy and complex evaluation process conducted by FDA scientists and its outside advisors, who assess reams of complex data on pharmacology and clinical trial results, not all of which are publicly available."[48] Public Citizen believes that stronger restrictions would better protect patients and urges the agency to strengthen its efforts to block promotion of drugs and medical devices for unapproved uses.

THE FIRST AMENDMENT

As the FDA is well aware, the pharmaceutical and medical device industries invoke the First Amendment to support their push to engage in increased promotion for unapproved uses. In our view, the First Amendment provides strong support for the existing regulatory regime and restrictions.

The pharmaceutical industry—most recently the drug company Amarin, supported by other members of the industry as *amici curiae*—has argued that federal laws and regulations providing that prescription drugs can be introduced in commerce only if intended for uses approved by the FDA are a form of content- and speaker-based regulation of speech. That proposition, if accepted, would grant a drug manufacturer the presumptive ability to promote and market a drug for any use once it has received FDA approval for a single use, with the burden on the FDA to prove that the manufacturer's marketing was deceptive or that the drug was unsafe for that use. But the implications do not stop there. Taken seriously, the proposition that introducing a substance into commerce for a particular purpose is speech fully protected by the First Amendment would imply that, unless it were otherwise unlawful to manufacture or sell a substance, a manufacturer could market that substance as a drug with no approval at all, and its conduct in so doing would receive First Amendment protection unless the government bore the burden of showing that prohibiting the marketing of the drug satisfied strict scrutiny. Such a result would overturn the carefully constructed, decades-old regulatory structure that governs pharmaceuticals, which is premised on the FDA's expertise in determining whether to permit marketing only of drugs that manufacturers have proven to be safe and effective for their intended use.

The heart of the federal regulatory regime governing prescription drugs since the 1962 amendments to the FDCA has been the requirement that manufacturers bear the burden of proving both the safety and effectiveness of their drugs to obtain FDA premarket approval to sell them:

[46] FDA. Memorandum, *supra* note 13, at 8-9.
[47] *Id.*
[48] Avorn J, Sarpatwari A, Kesselheim AS. Forbidden and Permitted Statements about Medications — Loosening the Rules. *N Engl J Med*. 2015;373(10):967-973.

> In 1962, Congress amended the FDCA and shifted the burden of proof from the FDA to the manufacturer. Before 1962, the agency had to prove harm to keep a drug out of the market, but the amendments required the manufacturer to demonstrate that its drug was "safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling" before it could distribute the drug. … In addition, the amendments required the manufacturer to prove the drug's effectiveness by introducing "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."[49]

The interlocking provisions of the FDCA and its implementing regulations establish that if a manufacturer places a drug into commerce with the intent that it be sold for an unapproved use, the manufacturer violates the FDCA's prohibition on introduction of an unapproved new drug.[50] Marketing a drug with such intent also violates the prohibition on misbranding a drug, because the drug's approved labeling will lack adequate directions for the unapproved use.[51]

As is generally true of a person's or company's intent, the intent with which a drug manufacturer introduces its products into commerce must be inferred, and a pharmaceutical company's statements in promoting its drugs are a primary source of evidence about its intent.[52] The industry contends, however, that because it will manifest that intent through commercial speech aimed at encouraging doctors to prescribe products for an unapproved use, its marketing is entitled to First Amendment protection. On this point, the industry often invokes the Second Circuit's decision in *United States v. Caronia*,[53] but the holding of *Caronia* was only that the FDCA does not outlaw promotional speech in and of itself. If it did, the court held, its application to the facts of that case would not have comported with the First Amendment.[54] The court took care not to hold that using speech to establish a pharmaceutical company's intent to introduce a drug into commerce for an unapproved use would violate the First Amendment—indeed, it explicitly stated its assumption that "such use of evidence of speech is permissible."[55] *Caronia*'s assumption was firmly grounded in the Supreme Court's holding in *Wisconsin v. Mitchell* that "[t]he First Amendment … does not prohibit the evidentiary use of speech to establish the elements of a crime or to prove motive or intent."[56]

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[49] *Wyeth v. Levine*, 555 U.S. 555, 567 (2009) (quoting provisions now codified at 21 U.S.C. § 355(d)).
[50] 21 U.S.C. §§ 331(d), 355(a).
[51] *See id.* §§ 331(a) & (b), 352(f)(1).
[52] *See United States v. An Article Consisting of 216 Cartoned Bottles, More or Less*, 409 F.2d 734, 739 (2d Cir. 1969) ("It is well settled that the intended use of a product may be determined from its label, accompanying labeling, promotional material, advertising and any other relevant source.").
[53] 703 F.3d 149 (2d Cir. 2012).
[54] *See id*. at 161–62.
[55] *Id*. at 162 n.9. The court further stated that it would be "unclear" whether a manufacturer's mere knowledge that a doctor intended to put a drug to an unapproved use would establish an illicit intent by the manufacturer in distributing the drug. 703 F.3d at 162 n.9.
[56] 508 U.S. 476, 489 (1993); *see also United States v. Pierce*, 785 F.3d 832, 841 (2d Cir. 2015); *United States v. Salameh*, 152 F.3d 88, 112 (2d Cir. 1998); *United States v. Kaziu*, 559 F. App'x. 32, 35 (2d Cir. 2014).

Even if restrictions on manufacturers' marketing of their products for unapproved uses were properly viewed as speech restrictions, the restrictions would pass muster as reasonable steps to advance the government's substantial interest in protecting and advancing public health by ensuring the safety and effectiveness of drugs and medical devices for each intended use.[57] This conclusion is bolstered significantly by the fact, discussed above, that so much of manufacturers' promotion for unapproved uses is misleading.

Some manufacturers have argued that the Supreme Court's decisions in *IMS v. Sorrell* and *Reed v. Town of Gilbert* suggest that restrictions on their commercial speech concerning drugs are subject to strict scrutiny under the First Amendment. Those cases, however, are inapposite. First, unlike the FDCA, the state law at issue in *Sorrell*, did not restrict the marketing of a product based on the marketer's intent; it *directly* restrained speech—the dissemination of information.[58] And *Reed* did not involve commercial speech but a local ordinance that allowed the posting of some temporary signs and barred others based on the content of the signs.[59]

Moreover, even if marketing a drug with the intent that it be put to an unapproved use were subject to First Amendment protection, it would not follow that *Sorrell* or *Reed* would command the application of strict scrutiny. *Sorrell* held that a law that placed content- and speaker-based burdens on pharmaceutical manufacturers' commercial speech was subject to what it called "heightened scrutiny," but the Supreme Court used that term to differentiate the scrutiny applicable in general to "expression protected by the Free Speech Clause of the First Amendment" from the rational-basis scrutiny applicable to non-speech economic regulation, which the state in *Sorrell* advocated.[60] The Court did not use the term "heightened scrutiny" to specify a particular level of First Amendment scrutiny. To the contrary, the Court declined to determine whether strict scrutiny or the intermediate scrutiny applicable to commercial speech applied to the law at issue because it held that the law could not be upheld under either standard.[61] *Reed*, for its part, said nothing about standards applicable to commercial speech. Subsequently, numerous courts have rejected the argument that *Sorrell* or *Reed* overturned established law that regulations of commercial speech are subject to a lesser standard of justification under the First Amendment than restrictions of non-commercial speech.[62]

The notion that the use of speech as evidence of someone's intent in distributing a product is not only subject to First Amendment scrutiny, but to strict scrutiny at that, would have broad consequences. Speech is used to discern intent, without First Amendment scrutiny, in a broad range of cases, including, among others, criminal conspiracy, antitrust, and employment

[57] *See Central Hudson*, 447 U.S. 557 (1980) (setting for standard for restrictions on commercial speech).
[58] 131 S. Ct. 2653, 2667 (2011).
[59] 135 S. Ct. 2218 (2015).
[60] 131 S. Ct. at 2659.
[61] *See id*. at 2667; *see also Caronia*, 703 F.3d at 164 (stating that *Sorrell* "did not decide the level of heightened scrutiny to be applied, that is, strict, intermediate, or some other form of heightened scrutiny").
[62] *See, e.g., Chiropractors United for Research & Educ., LLC v. Conway*, 2015 WL 5822721, at *5 (W.D. Ky. Oct. 1, 2015); *Contest Promotions, LLC v. City and Cty. of S.F.*, 2015 WL 4571564, at *4 (N.D. Cal. July 28, 2015); *California Outdoor Equity Partners v. City of Corona*, 2015 WL 4163346, at *10 (C.D. Cal. July 9, 2015); *King v. Gen. Info. Servs.*, 903 F. Supp. 2d 303, 307–09 (E.D. Pa. 2012).

discrimination cases. In particular, it is not unusual for a person's intent concerning the commercial use of an item to have consequences with respect to whether his conduct is lawful or unlawful. The Supreme Court, for example, recently considered the federal Controlled Substance Analogue Enforcement Act, which makes unlawful the knowing manufacture or distribution (or possession with intent to distribute) of a substance that is similar in chemical structure and physiological effect to a federally listed controlled substance if the substance is "intended for human consumption."[63] The Court held that a conviction under the Act requires that the jury find the defendant possessed knowledge that the substance was an analogue of a controlled substance as well as intent that it be used for human consumption.[64] Unsurprisingly, the Court's opinion suggests no discomfort with the First Amendment implications of making the defendant's guilt depend on his or her intent with respect to the purchaser's use of the substance.

Under the view of the First Amendment espoused by industry, however, the law would require First Amendment scrutiny if the government sought to prove a defendant's intent based on his or her statements that a buyer could get high if he or she used the analogue. Imposing liability where the defendant had promoted an analogue for such use but not where he or she had sold the substance for use as, say, an engine lubricant would be a "content-based" restriction on speech. And punishing a manufacturer or distributor who had advocated human consumption of a controlled substance analogue, but not a blogger who supported the use of the substance by humans, would, in industry's view, be a "speaker-based" speech regulation. A theory under which the use of speech to prove intent concerning the distribution of controlled substances would be subject to First Amendment scrutiny, let alone strict scrutiny, is dubious, to say the least.

As the FDA has recognized, the industry view of the First Amendment's scope would have extremely broad implications for drug and device regulation because it would call into question the foundation of the regulatory regime.[65] The regulatory regime is, at its most basic level, triggered by the introduction of a substance into commerce with the intent that it be used to diagnose, cure, mitigate, treat, or prevent disease or to affect the structure or function of the body.[66] It would, for example, be perfectly legal from the standpoint of the FDCA to introduce a new drug into commerce as an indoor plant food, without FDA review and approval: The FDCA would not classify the substance as a drug if sold with the intent that it be used in that manner, and, hence, it would not require FDA approval. The industry's First Amendment theory, however, suggests that if a manufacturer could lawfully market the substance for that non-drug use but could not, without approval, lawfully market it for use to prevent disease, the imposition of criminal or civil liability on the manufacturer for selling the product as a drug without

[63] *McFadden v. United States*, __ U.S. __, 2015 WL 2473377, at *4 (2015) (discussing 21 U.S.C. § 813).
[64] *See id*. at *5.
[65] *Amarin Pharma Inc. v United States Food & Drug Administration*, 119 F. Supp. 3d 196, 226 (S.D.N.Y. 2015) (quoting FDA brief and FDA statement at oral argument).
[66] *See 216 Cartoned Bottles*, 409 F.2d at 739 ("Regardless of the actual physical effect of a product, it will be deemed a drug for purposes of the Act where the labeling and promotional claims show intended uses that bring it within the drug definition."); *see also, e.g.*, *Whitaker v. Thompson*, 353 F.3d 947, 949–52 (D.C. Cir. 2004); *United States v. Cole*, __ F.3d __, 2015 WL 471594, at *3 (D. Or. Feb. 5, 2015); *United States v. Livdahl*, 459 F. Supp. 2d 1255, 1259–60 (S.D. Fla. 2005).

approval would require First Amendment scrutiny because liability would be based on the manufacturer's speech in promoting the product as a drug.[67] Moreover, according to some industry arguments, the prohibition on selling an unapproved drug as a drug rather than as fertilizer would be subject to strict scrutiny, under which, they argue, the burden would be on the FDA to prove that the unapproved substance posed dangers that were sufficient to create a compelling interest in stopping the manufacturer from marketing it as a drug.

Assertions that the FDCA's fundamental requirement of premarket approval violates the First Amendment because it is based on an inference of intent from the manner in which a manufacturer markets a product have, when made directly, been rejected by the courts.[68] The FDA should not allow expanded promotion for unapproved uses based on that argument. Such expansion is not constitutionally required and would be detrimental to important protections for public health and safety. The FDCA's requirement that manufacturers bear the burden of proving both the safety and effectiveness of new drugs for their intended uses is *critical* to achieving Congress's objectives of protecting the public against unsafe or worthless pharmaceutical products.

Last year, the judge presiding over the *Amarin Pharma* litigation suggested that the current drug-approval framework may be inconsistent with "modern First Amendment law."[69] That judge's worrisome suggestion is not correct. The First Amendment provides no protection to commercial speech—speech that proposes a commercial transaction—if that speech is false or misleading. And messages promoting unapproved uses are necessarily misleading when they suggest a health benefit that has not been established. Even beyond the misleading nature of much off-label promotion, the First Amendment is no bar to commercial speech restrictions that advance substantial government interests. The FDCA regulatory scheme, and in particular the drug-approval process, was developed over the 20th Century to protect a very substantial government interest: protecting public health. The First Amendment view set forth in the *Amarin* decision fails to understand the balancing that is at the very heart of First Amendment cases and the invaluable role of the regulatory scheme in protecting patients from unsafe or ineffective drugs.

CONCLUSION

History shows that after-the-fact enforcement is inadequate to protect patient safety. Rather, when an unproven assertion of safety and effectiveness is relied on, the resulting harm may be severe—even, as was the case with Elixir Sulfanilamide, irreparable. In the strongest

[67] *Cf. Caronia*, 703 F.3d at 180 (Livingston, J., dissenting).
[68] *See Whitaker*, 353 F.3d at 953; *United States v. Cole*, 2015 WL 471594, at *4–5; *see also Holistic Candlers & Consumer Ass'n v. FDA*, 770 F. Supp. 2d 156, 164 & n.15 (D.D.C. 2011) (characterizing First Amendment challenge to requirement of premarket approval for medical device as "foreclosed by settled law holding that use of speech to establish an element of a violation does not violate the First Amendment"), *aff'd on other grounds*, 664 F.3d 940 (D.C. Cir. 2012).
[69] *Amarin Pharma Inc. v United States Food & Drug Administration*, 119 F. Supp. 3d at 226.

terms, we urge the FDA to strengthen, not loosen, its restrictions on promotion of drugs and medical devices for unapproved uses.

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