UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

ALLERGAN, INC., Plaintiff, v. UNITED STATES OF AMERICA, UNITED STATES FOOD AND DRUG ADMINISTRATION; DR. MARGARET HAMBURG, Commissioner of the United States Food and Drug Administration; and KATHLEEN SEBELIUS, Secretary of the United States Department of Health & Human Services, Defendants.	Civil Action No. 1:09-cv-01879 (JDB)

MEMORANDUM OF PUBLIC CITIZEN AS AMICUS CURIAE IN SUPPORT OF DEFENDANTS' MOTION FOR SUMMARY JUDGMENT AND IN OPPOSITION TO PLAINTIFF'S MOTION FOR A PRELIMINARY INJUNCTION

Gregory A. Beck (DC Bar # 494479)
Allison M. Zieve (DC Bar # 424786)
Public Citizen Litigation Group
1600 20th Street NW
Washington, DC 20009
202-588-1000

Counsel for Amicus Curiae Public Citizen

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INTRODUCTION

This case involves plaintiff Allergan, Inc.'s claim of a constitutional right to promote its drug for uses that have not been determined by the Food and Drug Administration (FDA) to be safe and effective—referred to as "off-label uses." If successful, Allergan's claim would allow it and other drug companies to bypass the federal system of pre-market safety and effectiveness review and return the nation to the days of snake-oil salesmen, when products were regularly promoted with unproved, exaggerated, or fraudulent health claims. Specifically, Allergan wishes to promote unapproved uses of a nerve toxin that, particularly when administered for some off-label conditions, can spread throughout the body, causing paralysis and death. The First Amendment does not give Allergan the right to promote a dangerous product in contravention of laws established to protect patient health. The defendants' motion for summary judgment should be granted, and Allergan's motion for a preliminary injunction should be denied.

INTERESTS OF AMICUS CURIAE

Amicus Public Citizen is a non-profit membership organization with a longstanding interest in public health, including drug safety and FDA regulation. Public Citizen's Health Research Group (HRG) promotes research-based, system-wide changes in health care policy and provides oversight concerning drugs and medical devices, among other things. In January 2008, Public Citizen HRG filed a citizen petition with the FDA seeking additional warnings on Botox and other products containing botulinum toxin. The FDA granted that petition in large part, requiring a boxed warning (the strongest warning it can require), a letter to doctors, and a medication guide to be handed to patients warning that the toxin can spread from the point of injection and cause life-threatening swallowing and breathing problems. Public Citizen therefore has substantial experience with both the factual and regulatory background of this case.

In addition to its interest in drug regulation and health issues, Public Citizen has significant interest and expertise in commercial speech doctrine. Public Citizen believes that the framework for judging restraints on commercial speech developed by the Supreme Court in *Central Hudson Gas & Electric Corp. v. Public Service Comm'n*, 447 U.S. 557 (1980), strikes an appropriate balance between safeguarding the free speech rights of commercial actors and preserving the government's ability to prevent harm to consumers. Public Citizen has represented parties seeking to invalidate overbroad restraints on commercial speech when those restraints harmed competition and injured consumers, including in *Virginia State Board of Pharmacy v. Virginia Citizens Consumer Council, Inc.*, 425 U.S. 748 (1976), *Zauderer v. Office of Disciplinary Counsel*, 471 U.S. 626 (1985), and *Edenfield v. Fane*, 507 U.S. 761 (1993). It has also defended commercial-speech restrictions in cases where the restrictions were important to protecting the public health or served other important state interests, for example in *Lorillard Tobacco Co. v. Reilly*, 533 U.S. 525, 561 (2001). Public Citizen offers a consumer perspective on the commercial-speech balancing process, different from that of either of the parties.

STATUTORY BACKGROUND

Allergan challenges statutory and regulatory provisions prohibiting drug companies from promoting a particular use of a drug until the FDA has approved that use. *See* 21 U.S.C. §§ 331(d), 355(a). The pre-market approval requirement is a key part of the Food, Drug, and Cosmetic Act (FDCA) and the regulatory scheme designed to ensure the safety and effectiveness of drugs. To understand Allergan's challenge to the approval process, it is necessary to understand the details of the regulatory scheme in which that process is contained.

Congress established the first meaningful federal drug regulation in the Food and Drugs Act of 1906. The 1906 Act was a response to widespread fraudulent "patent medicine" schemes that promised cures for nearly any illness. Wallace F. Janssen, *Outline of the History of U.S.*

Drug Regulation & Labeling, 36 Food Drug Cosm. L.J. 420, 422 (1981). The law gave the federal government authority to protect consumers by seizing adulterated or misbranded drugs, including drugs with labeling that is "false or misleading in any particular." 21 U.S.C. § 352(a). The 1906 law, however, did not require drug companies to perform any tests or submit any evidence to the FDA before promoting their drugs to the public, Richard A. Merrill, *The Architecture of Government Regulation of Medical Products*, 82 Va. L. Rev. 1753, 1761 (1996), but limited the FDA's enforcement authority to drugs that were already on the market. *Id.*

The lack of a pre-market approval process led to a public outcry in 1937, when a tainted antibiotic that the drug's manufacturer had never tested for safety killed more than one hundred people. *Id*. In response to the disaster, Congress passed the Food, Drug, and Cosmetic Act of 1938. *Id.* at 1761-62. 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 "substantial evidence" that the drug is safe for "use under the conditions prescribed" in its labeling. 21 U.S.C. §§ 321(p), 355(a), (b), (d). The law thus prohibited, for the first time, marketing a drug for any use not approved by the FDA.

In 1962, Congress enacted the next major amendment to the FDCA, this time inspired by the Thalidomide tragedy. Thalidomide, prescribed to pregnant women in Europe as a treatment for morning sickness, caused birth defects in hundreds of babies. Kept off the U.S. market by the vigilance of an FDA medical officer, the tragedy sparked congressional hearings, which revealed that drug companies were making effectiveness claims that were unsupported or based on shoddy scientific evidence. FDA, *Promoting Safe and Effective Drugs for 100 Years*, http://www.fda.gov/AboutFDA/WhatWeDo/History/CentennialofFDA/CentennialEditionofFDA

Consumer/ucm093787.htm. The 1962 amendments require an NDA to include substantial evidence not only of a drug's safety, but also of its effectiveness for each intended use. 21 U.S.C. §§ 321(p), 355(a), (b), (d). This evidence must be supported by "adequate and well-controlled investigations." *Id.* § 355(d). 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 promoting the drug for that new use. *See* 21 C.F.R. § 314.70. In this way, the regulatory scheme is crafted to provide an objective assessment of safety and effectiveness for *each* use for which the manufacturer intends to promote its product, *before* the manufacturer promotes the drug for patients' use.

ARGUMENT

Drug makers use a wide variety of methods to promote their drugs to doctors, including office visits, sponsorship of seminars, conferences, educational events, and distribution of article and textbook reprints. The self-evident purpose of many of these communications is to sell more of the companies' products. Such communications constitute commercial speech because they do "no more than propose a commercial transaction." *Bolger v. Youngs Drug Prods. Corp.*, 463 U.S. 60, 66 (1983). Even when a drug company's message is contained in seemingly neutral media, such as journal articles and seminars, the communications are nevertheless commercial because they "reference . . . a specific product" and the companies have "an economic motivation" for making them. *Id.* The underlying, if implicit, message of these communications is that "a physician should prescribe—and a consumer therefore will purchase—the subject drug." *Wash. Legal Found. v. Friedman*, 13 F. Supp. 2d 51, 64 (D.D.C. 1998), *vacated on other grounds*, *Wash. Legal Found. v. Henney*, 202 F.3d 331 (D.C. Cir. 2000). Although the commercial speech may be "intertwined" with non-commercial elements, the communication as a whole

is still commercial. *See Bd. of Trs. of State Univ. of N.Y. v. Fox*, 492 U.S. 469, 473 (1989); *see also Bolger*, 463 U.S. at 67-68 (holding that "mailings constitute[d] commercial speech notwithstanding the fact that they contain[ed] discussions of important public issues").

Restrictions on commercial speech such as those at issue here are evaluated under the test the Supreme Court first set forth in *Central Hudson*, 447 U.S. 557. The *Central Hudson* test carefully balances the First Amendment rights of commercial actors and the government's compelling interest in protecting the public. Assuming that the restricted communication is not misleading and does not advertise an unlawful activity, a regulation survives the *Central Hudson* test if the government can show that "the asserted governmental interest is substantial" and that the regulation both "directly advances the governmental interest asserted" and "is not more extensive than is necessary to serve that interest." *Thompson v. W. States Med. Ctr.,* 535 U.S. 357, 367 (2002) (internal quotation omitted). Because the system of pre-market approval of each intended use and the related restriction on promoting drugs for unapproved uses are essential components of the FDA's ability to protect patients from dangerous drugs and fraudulent claims, the challenged regulatory provisions easily satisfy the *Central Hudson* test.[1]

I. The Government's Interest Is at Its Peak When Protecting the Public from Dangerous Prescription Drugs and Fraudulent Health Claims.

The first prong of *Central Hudson* requires the government to identify a substantial interest in support of its regulation. *Id.* Here, as the Supreme Court has recognized, "[p]reserving the effectiveness and integrity of the [FDA's] . . . drug approval process is clearly an important gov-

[1] False and misleading speech may be banned outright, without engaging in the balancing test used to evaluate restrictions on truthful, non-misleading speech. *Central Hudson*, 447 U.S. at 563-64. Promotion of unapproved uses is often misleading because it suggests a level of scientific certainty that does not exist. However, because this Court has previously analyzed off-label promotion under the three-part *Central Hudson* balancing test, *see Friedman*, 13 F. Supp. 2d at 66, we do so as well in this memorandum.

ernmental interest." *Id.* at 369. The pre-market approval process is a cornerstone of modern health and safety regulation, serving the separate but complementary goals of protecting the public from dangerous drugs and preventing false and misleading claims. *See Abigail Alliance for Better Access to Dev'l Drugs v. von Eschenbach*, 495 F.3d 695, 703 (D.C. Cir. 2007) (en banc). Indeed, "[t]here are few, if any, more important functions performed by any regulatory agency than the function this case concerns—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." *See Friedman*, 13 F. Supp. 2d at 69.

The preeminent purpose of the NDA approval process is to protect the public from unsafe or ineffective drugs. *See* 21 U.S.C. § 393(b) (defining FDA mission as to "protect the public health"); *United States v. Lane Labs-USA Inc.*, 427 F.3d 219, 227 (3d Cir. 2005) ("[P]rotecting consumer health and safety is a primary purpose of the FDCA."). And the driving force behind both the 1938 and 1962 laws, which together established the system of FDA pre-market review of drug safety and effectiveness, was significant injuries and deaths caused by dangerous drugs. *See* Merrill, 82 Va. L. Rev. at 1761-62. Through the NDA and supplemental NDA process, Congress sought to protect patients by detecting unsafe or ineffective medicines *before* they could be distributed to the public. *See* 21 U.S.C. § 321(p) (defining a "new drug" as a drug "not generally recognized among experts . . . as safe and effective for use"). The government's interest is at its maximum when protecting the health and safety of the public from products, such as drugs, that can injure or kill. *See Abigail Alliance*, 495 F.3d at 713 (recognizing the government interest in "protecting patients . . . from potentially unsafe drugs with unknown therapeutic effects").

In addition, "there is no question that [the government's] interest in ensuring the accuracy of commercial information in the marketplace is substantial." *See Edenfield*, 507 U.S. at 768-69.

The regulatory scheme protects consumers from false and misleading health claims. *See* 21 U.S.C. § 355(d); *see also* 21 U.S.C. § 331 (prohibiting misbranding of drugs); 21 U.S.C. § 352 (defining "misbranded drugs" to include any drugs labeled or packaged in a misleading manner). Pre-market review for effectiveness protects the government's compelling interest in ensuring that consumers get what they pay for when they purchase prescription drugs. *See Lane Labs*, 427 F.3d at 227 ("Preventing such deception has as much to do with ensuring customers receive the value they expect from products as it does ensuring their safety."); *see also Va. State Bd. of Pharmacy*, 425 U.S. at 771-72 ("The First Amendment . . . does not prohibit the State from insuring that the stream of commercial information flow cleanly as well as freely.").

Each of these interests satisfies the first *Central Hudson* prong. Allergan seems to agree. *See* Allergan Prelim. Inj. Mem. at 22 ("[T]he Government concededly has a substantial interest in '[p]reserving the effectiveness and integrity of the Act's new drug approval process' by providing incentives for manufacturers to seek FDA approval for new uses of previously approved drugs, and thus to subject new uses to the rigorous testing that new drugs must undergo.") (citations omitted).

II. Pre-Market Scrutiny of Safety and Effectiveness and Restrictions on Off-label Promotion of Uses That Have Not Obtained FDA Approval Directly Advance the Government's Interest in Protecting Consumers.

The next step of the *Central Hudson* test requires the government to "demonstrate that the challenged regulation advances the Government's interest in a direct and material way." *Fla. Bar v. Went For It, Inc.*, 515 U.S. 618, 624 (1995). Here, the regulations at issue directly protect the public by requiring a drug manufacturer, as a condition for sale in interstate commerce, to provide "substantial evidence" that its drug is both safe and effective for *each* intended use *before* promoting the drug for that use. 21 U.S.C. §§ 321(p), 355(a), (b), (d), (j).

To meet the "substantial evidence" standard, a drug company must provide "evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved." *Id.* § 355(d). These standards "express well-established principles of scientific investigation," and the Supreme Court has held them "amply justified by the legislative history." *Weinberger v. Hynson, Westcott & Dunning, Inc.*, 412 U.S. 609, 619 (1973). The statutory standard is further fleshed out by FDA regulations setting forth principles "recognized by the scientific community as the essentials of an adequate and well-controlled clinical investigation." 21 C.F.R. § 314.126(a). These include steps to minimize bias, ensure selection of appropriate subjects and adequate controls, and exclude "[i]solated case reports, random experience, and reports lacking the details which permit scientific evaluation." *Id.* § 314.126(a), (b), (d), (e).

Allergan complains that the regulatory scheme prohibits it from making claims even when it has evidence in its possession that those claims are true. If it has such evidence, however, the statute and regulations provide a frequently used route to promoting its claims: submission of a supplemental NDA for FDA review. *See* 21 C.F.R. § 314.70. Rather than relying on drug companies' unsubstantiated assertions, Congress and the FDA require drug companies to *prove* to an objective decisionmaker—the FDA—that their drugs are safe and effective for particular uses. The pre-market review process is a crucial bulwark against the sorts of pseudo-scientific evidence that was a hallmark of fraudulent medicine before the era of federal drug regulation. *See* Janssen, 36 Food Drug Cosm. L.J. at 422. The challenged regulatory scheme thus reflects Congress's and the FDA's reasonable conclusion that advertising drugs for uses not validated by science is false or misleading and that, in light of the history of snake-oil salesmen touting products based on fraudulent or unproved claims, a system of objective scientific evaluation is

needed to protect consumers. *See Bates v. State Bar of Ariz.*, 433 U.S. 350, 366 (1976) (noting that claims that are "not susceptible of precise measurement or verification . . . might well be deceptive or misleading to the public, or even false").

The regulatory scheme also reflects Congress's judgment that FDA review is needed before, rather than after, drug companies begin promoting drugs for new uses. That judgment is based on the experience that, in the absence of prior review, consumers could be injured or killed before the FDA has had a chance to discover that a drug is dangerous. Even where life and health is not at stake, the Supreme Court has expressed approval for rules requiring filing and preapproval of advertisements. *See Central Hudson*, 447 U.S. at 571 n.13 (recommending a state preview advertising campaigns as a less restrictive alternative to banning speech); *Shapero v. Ky. Bar Ass'n*, 486 U.S. 466, 476 (1988) (noting that the state could require lawyers to file advertisements with the state bar); *In re R.M.J.*, 455 U.S. 191, 206 (1982) (same). The need for preapproval is especially compelling here because drug regulations "touch phases of the lives and health of people which, in the circumstances of modern industrialism, are largely beyond self-protection." *United States v. Dotterweich*, 320 U.S. 277, 280 (1943). Patients lack both the expertise and the means to engage in the expensive and time-consuming process of evaluating drugs for safety and effectiveness, and physicians have neither time nor adequate data to make such an evaluation in the first instance. It therefore falls to the government to do so.

To be sure, any system of pre-clearance imposes some delay. But Congress and the FDA have judged the delay to be justified by the resulting ability to ensure that drugs on the market are safe and effective. The *Central Hudson* standard is not an invitation to second-guess that judgment. Within the bounds of reasonableness, the courts "leave it to governmental decision makers to judge what manner of regulation may best be employed." *Fox*, 492 U.S. at 480; *see*

also United States v. Edge Broad. Co., 509 U.S. 418, 434 (1993) ("Within the bounds of the general protection provided by the Constitution to commercial speech, we allow room for legislative judgments."). Here, as the expert agency, the FDA is entitled to substantial deference when it construes its governing statutes, including those implementing the pre-market approval rule. *See Young v. Cmty. Nutrition Inst.*, 476 U.S. 974, 980-81 (1986); *Cont'l Air Lines, Inc. v. Dep't of Transp.*, 843 F.2d 1444, 1448-54 (D.C. Cir. 1988). Moreover, courts give special deference to Congress when it exercises "its well-established power to regulate in response to scientific, mathematic, and medical advances" because Congress is better situated than the courts to keep up with rapid advances in those areas. *Abigail Alliance*, 495 F.3d at 706. Congress is also best situated to balance the competing interests of "early availability of products to patients . . . and the need to obtain sufficient data to provide a reasonable expectation of benefit and lack of excessive harm." *Id.* at 700.[2]

Allergan is wrong to suggest that, once the FDA has approved a drug for one particular use, the government lacks an interest in evaluating the drug's safety for additional uses. The FDA does not evaluate safety in a vacuum—as to each proposed use, the agency must balance the drug's risks against its benefits for that use. *See* Richard A. Merrill, *Risk-Benefit Decision-making by the FDA*, 45 Geo. Wash. L. Rev. 994 (1977). For example, a drug that poses a serious risk to the patient's immune system may warrant approval to treat cancer if the risk is offset by

[2] *See also Gonzales v. Carhart*, 550 U.S. 124, 127 (2007) ("The Court has given state and federal legislatures wide discretion to pass legislation in areas where there is medical and scientific uncertainty."); *Greenwood v. United States*, 350 U.S. 366, 375-76 (1956) (holding that courts should not deny Congress the constitutional power to deal with a situation where "science has not reached finality of judgment"); *Jacobson v. Massachusetts*, 197 U.S. 11, 30-31 (1905) (holding that, in the face of uncertain evidence, the Massachusetts legislature was entitled to decide a matter of public health "in the light of all the information it had or could obtain"); *Abigail Alliance*, 495 F.3d at 713 ("Our Nation's history and traditions have consistently demonstrated that the democratic branches are better suited to decide the proper balance between the uncertain risks and benefits of medical technology, and are entitled to deference in doing so.").

the benefits of its effect on cancer, but not warrant approval to treat a headache. Moreover, Allergan's argument overlooks the government's interest in ensuring that a drug is not only safe, but *effective* for every intended use. Even if a drug is relatively safe for a particular unapproved use, a drug company's promotion of the product for that use can have serious health effects if it diverts a patient from a more effective treatment. *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).

In any event, 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 can cause stroke when used to suppress lactation in post-partum women. *See* 59 Fed. Reg. 43347 (1994) (FDA notice of withdrawal of approval for use to suppress lactation); Novartis, *Parlodel*, http://www.pharma.us.novartis.com/product/pi/pdf/parlodel.pdf, at 3-4 (current product labeling, listing approved uses).

Hormone replacement drugs provide another example. Throughout the 1990s, doctors prescribed hormone replacement drugs to women as a preventative measure against a range of illnesses, including heart disease, breast cancer, and Alzheimer's disease. G. Kolata and M. Petersen, *Hormone Replacement Study a Shock to the Medical System*, N.Y. Times, July 10, 2002, at A1. Although the FDA had approved hormone replacement drugs for treating specific symptoms associated with menopause, such as hot flashes, it had not approved the drugs for these other uses. *Id.* After millions of prescriptions had been written—including for many women who had not even entered menopause—a large government-funded study found that use of the drugs actually *increased* women's risk of developing some of the very health problems the drugs were

supposed to treat. *Id.* Unfortunately, bromocriptine and hormone replacement drugs are just two of many examples. *See also*, *e.g.*, *Perry v. Novartis Pharms. 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); *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).

III. The Challenged Regulations Are No Broader than Necessary to Accomplish the Government's Substantial Interest.

The final step of *Central Hudson* requires a reasonable "'fit' between the legislature's ends and the means chosen to accomplish those ends." *Went For It*, 515 U.S. at 624. The means chosen need not be "the single best disposition" and the fit need not be "perfect." *Fox*, 492 U.S. at 480. Rather, the government must show only that its chosen restrictions are reasonable—that is, reasonably in proportion to the interest served. *See Went For It*, 515 U.S. at 633 (prohibition must be "reasonably well tailored to its stated objective"). Although the government cannot satisfy its evidentiary burden with "mere speculation or conjecture," the Supreme Court has recognized that the government's showing need not be "accompanied by a surfeit of background information." *Id.* at 628. The regulatory scheme easily satisfies these standards here.

1. To begin with, the FDCA and FDA regulations do not totally prohibit Allergan from making claims about the safety and effectiveness of its product. The regulatory scheme requires only that Allergan allow the FDA to assess the validity of the company's claims before it makes those claims to doctors. In the absence of this neutral review requirement, drug companies have no incentive to assemble competent evidence that their drugs are safe and effective for more than one use. Indeed, allowing promotion of unapproved uses would create a perverse incentive for

drug manufacturers to seek approval for only the narrowest and most easily established use of any particular drug. Once the drug was approved for a single use, the company could promote it for any uses it chose, with little reason to seriously investigate the drug's safety and effectiveness as to the additional uses. *See* Aaron S. Kesselheim & Jerry Avorn, *Pharmaceutical Promotion to Physicians and First Amendment Rights*, 358 New Eng. J. Med., Apr. 17, 2008, at 1727. The result would be less research about the drug and, therefore, less information for patients and doctors.

Allergan complains that the restrictions limiting promotion while an application is pending leave it "no clearly lawful avenue" to communicate information about off-label use. Allergan Prelim. Inj. Mem. at 2. To begin with, Allergan assumes that submitting a supplemental NDA to the FDA establishes the safety and effectiveness of additional uses and that FDA approval of the supplemental NDA is a foregone conclusion. In fact, safety and effectiveness is not established when a company submits an application, but when the FDA approves it, if the FDA approves it—which the agency may or may not do. Moreover, the absence of any way to circumvent the regulatory scheme demonstrates only that the scheme is effective at accomplishing its purpose. The First Amendment does not require regulations to contain easily exploitable loopholes to survive constitutional scrutiny. Indeed, if such loopholes existed, Allergan would undoubtedly argue that the scheme was unconstitutional on the ground that it was underinclusive and thus failed to accomplish the FDA's objectives. *See Rubin v. Coors Brewing Co.*, 514 U.S. 476, 489 (1995) (holding that "exemptions and inconsistencies" in a challenged regulation "bring into question the [regulation's] purpose," and concluding that the regulation "cannot directly and materially advance its asserted interest because of [its] overall irrationality"); *City of Cincinnati*

v. Discovery Network, 507 U.S. 410, 412 (1993) (finding a commercial speech violation where the challenged law addressed only a portion of the problem).

Allergan also argues that Congress could avoid restricting speech by prohibiting prescriptions for off-label use altogether, rather than prohibiting promotion of those uses. Regardless of whether Congress permits physicians to prescribe off-label drugs, however, Allergan has no legitimate interest in promoting drugs for purposes that it cannot substantiate with evidence of safety and effectiveness. In addition, as Allergan points out, the FDA cannot restrict off-label prescriptions because it has no authority over physicians. *See* S. Rep. No. 361, 74th Cong., 1st Sess. 3 (1935) ("[T]he bill is not intended as a medical practices act and will not interfere with the practice of the healing art."). As the Supreme Court has observed, the FDA's regulation of promotion rather than prescriptions is "an accepted and necessary corollary of the FDA's mission to regulate in this area without directly interfering with the practice of medicine." *Buckman Co. v. Plaintiffs' Legal Comm.*, 531 U.S. 341, 349-50 (2001). Doctors, unlike drug companies, have an independent professional duty to patients and, for the most part, lack an incentive to promote one drug over another. The pre-market clearance rules protect consumers while avoiding interference with the doctor-patient relationship. *See also United States v. Algon Chem. Inc.*, 879 F.2d 1154, 1163 (3d Cir. 1989) ("Congress exempted the practice of medicine from the [FDCA] so as not to limit a physician's ability to treat his patients.").

2. Allergan takes particular issue with the FDA's construction of the word "labeling." Congress defined the term to mean "written, printed, or graphic matter" on a drug, on its "containers or wrappers," or on other material "accompanying such article." 21 U.S.C. § 321(k), (m). The FDA's implementing regulations interpret this definition to include materials, such as brochures, booklets, article reprints, and "similar pieces of printed, audio, or visual matter descrip-

tive of a drug" that contain drug information "supplied by" and "disseminated by or on behalf" of a drug manufacturer. 21 C.F.R. § 202.1(*l*)(2).

Allergan reads "labeling" narrowly to include only materials that are integrated with a shipment of drugs. So interpreted, however, drug companies could easily circumvent the regulatory scheme by separating drugs from promotional materials. For precisely this reason, the Supreme Court in *Kordel v. United States* concluded that "the phrase 'accompanying such article' is not restricted to labels that are on or in the article or package that is transported." 335 U.S. 345, 349 (1948). The Court noted that it would "create an obviously wide loophole to hold that these drugs would be misbranded if the literature had been shipped in the same container but not misbranded if the literature left in the next or in the preceding mail," and that such a holding would defeat "[t]he high purpose of the Act to protect consumers who under present conditions are largely unable to protect themselves in this field." *Id.*; *see also United States v. Urbuteit*, 335 U.S. 355, 357-58 (1948) ("The Act is not concerned with the purification of the stream of commerce in the abstract. The problem is a practical one of consumer protection, not dialectics.").

3. Moreover, Allergan's argument fails to account for the drug industry's long history of evading the restrictions on promoting products for unapproved uses. For decades, the FDA has battled drug companies as they devised increasingly clever ways to promote unapproved uses of their drugs to doctors. Drug companies in recent years have used disguised advertising in the form of article reprints and textbook excerpts, seminars, conferences, and continuing education events to promote off-label use to doctors. *Henney*, 202 F.3d at 333 ("[M]anufacturers have sought to employ more indirect methods of informing physicians about their products' off-label uses."). These methods have become "an effective means of influencing physicians to prescribe a drug for a given condition." *Friedman*, 13 F. Supp. 2d at 70. Extensive evidence demonstrates

that companies exploit these techniques to deceive doctors about the safety and effectiveness of off-label uses.

For example, when selecting the educational material to send to doctors or to present at seminars, drug manufacturers choose material that plays up positive results and omits information about side-effects, adverse reactions, and warnings. Mark A. Ford, *Another Use of OxyContin: The Case for Enhancing Liability for Off-Label Drug Marketing*, 83 B.U. L. Rev. 429, 434 (2003); *see also Friedman*, 13 F. Supp. 2d at 65 (noting that "manufacturers will likely only seek to disseminate information that presents their product in a favorable light"). Companies may also present doctors with the results of preliminary studies with small sample sizes when the results reflect favorably on their drugs, while ignoring even well-documented studies showing the opposite, negative result. *Friedman*, 13 F. Supp. 2d at 65. Doctors are thus "led to believe that a certain drug is safe and effective because a manufacturer has found, and aggressively promoted, 'the one' article that supports use of their drug, even if there exists considerable evidence to the contrary." *Id.*

These methods are particularly deceptive because drug studies are overwhelmingly funded by the drug companies themselves. Editorial, *Sponsorship, Authorship, and Accountability*, 345 New Eng. J. Med., Sept. 13, 2001, at 825. The studies thus often lack the objectivity on which reliable medical research is based. *Id.* Even worse, the inherent bias may be hidden by drug companies that hire ghostwriters or recruit academics to pose as authors. Joseph S. Ross, et al., *Guest Authorship and Ghostwriting in Publications Related to Rofecoxib*, J. Am. Med. Ass'n, Apr. 16, 2008, at 1800-12. Merck, for example, funded a clinical study of Vioxx that appeared to test the safety of the drug but was actually designed and run by the company's marketing department to promote sales. Kevin P. Hill, et al., *The ADVANTAGE Seeding Trial: A Review of*

Internal Documents, Annals of Internal Med., Aug. 19, 2008, at 251-58. Merck did not disclose to the study participants or the publishing journal that the study was a marketing exercise. *Id.* Similarly, 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. *See* C. Seth Landefeld & Michael A. Steinman, *The Neurontin Legacy—Marketing through Misinformation and Manipulation*, 360 New Eng. J. Med., Jan. 8, 2009, at 103-06 (Parke-Davis engaged in 'the systematic use of deception and misinformation to create a biased evidence base and manipulate physicians' beliefs and prescribing behaviors.").

As the primary authors of studies, drug companies also have the ability to suppress unfavorable results. As a recent study found, drug companies selectively report the outcomes of random trials. S. Swaroop Vedula, et al., *Outcome Reporting in Industry-Sponsored Trials of Gabapentin for Off-Label Use*, 361 New Eng. J. Med., Nov. 12, 2009, at 1963-71. Unsurprisingly, the studies drug companies choose not to publish overwhelmingly report negative or questionable results. Erick H. Turner, et al., *Selective Publication of Antidepressant Trials and Its Influence on Apparent Efficacy*, 358 New Eng. J. Med., Jan. 17, 2008, at 252-60. In 2004, for example, Merck withdrew Vioxx from the market after revelations 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. Cecily Walters, *Researchers Reveal Merck's Ghostwritten Vioxx Studies*, Trial, July 2008.

Moreover, Allergan is wrong that the regulatory scheme excludes it from discussing its drug in scientific and academic literature and in public discourse. Drug companies are not prohibited from continuing to fund research, publishing their results, and generally engaging in

public discussion about their drugs, as long as they do not use these forms of communication to promote off-label uses. FDA, *Guidance for Industry: Good Reprint Practices for the Distribution of Medical Journal Articles and Medical or Scientific Reference Publications on Unapproved New Uses of Approved Drugs and Approved or Cleared Medical Devices* (Jan. 2009), *available at* http://www.fda.gov/oc/op/goodreprint.html. The FDA recognizes that "dissemination of truthful and non-misleading medical journal articles and medical or scientific reference publications on unapproved uses of approved drugs" is sometimes appropriate. *Id.* Accordingly, the FDA allows drug companies to distribute reprints of journal articles and reference publications to doctors if the reprints are unbiased and scientifically valid. *Id.*

The FDA's current guidelines allow drug companies to engage in public discourse and scientific debate, while addressing the most common problems resulting from unregulated off-label promotion. For example, the guidelines address the problem of incomplete, skewed, or biased data by stating that reprints should be accompanied by a disclosure identifying any conflicts of interest, *id.,* and by limiting a manufacturer's distribution of publications funded by, written at the request of, or influenced by the manufacturer. *Id.* They also include additional protections designed to insure 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. *Id.*

Importantly, Congress and the FDA did not adopt the supplemental NDA requirement and the definition of labeling as a "first resort," without exploring the feasibility of other options. *See Thompson*, 535 U.S. at 373. Rather, the regulatory scheme developed incrementally, in reaction to specific marketplace abuses, and directly and narrowly addresses the most common methods for circumventing regulatory requirements through off-label drug promotion. The Su-

preme Court has upheld commercial speech restrictions that are supported by a record of prior abuse, even when the restrictions have prohibited some truthful speech. *See Went for It*, 515 U.S. at 618 (holding that historical evidence of abuse may justify broad prophylactic restraints on speech); *Ohralik v. Ohio State Bar Ass'n*, 436 U.S. 447 (1978) (same). Especially given the substantial deference due to Congress and the FDA in matters of health and safety regulation, the regulations here are more than justified by the documented history of the drug industry's marketing practices. *Cf. United States v. Rutherford*, 442 U.S. 544, 558 (1979) (noting that the history of "resourceful entrepreneurs" peddling fraudulent cancer cures "suggest[s] why Congress could reasonably have determined to protect the terminally ill . . . from the vast range of self-styled panaceas that inventive minds can devise").

IV. Allergan's Own Product Highlights the Importance of the FDA's Pre-Market Review.

The serious health risks presented if the FDA were enjoined from enforcing the FDCA's supplemental NDA requirement and restrictions on off-label promotion that are an integral part of the regulatory scheme are amply illustrated by Allergan's own product, Botox. Botox is a formulation of botulinum toxin, a nerve poison produced by the bacteria responsible for botulism. CDC, *Botulism*, *available at* http://www.cdc.gov/nczved/dfbmd/disease_listing/botulism_gi.html (updated May 21, 2008). The toxin acts by blocking the transmission of nerve impulses, causing a loss of muscle control. *Id.* When acquired through contaminated food, the toxin can spread throughout the body, causing slurred speech, blurry vision, drooping eyelids, and muscle weakness. *Id.* The toxin can also cause paralysis of the esophagus, which can result in difficulty swallowing, reflux of food and drink, aspiration pneumonia, and, occasionally, death. *Id.* Even if treated early, recovery takes many weeks. *Id.* Serious cases can require months of intensive medical care or may result in death by paralysis of the respiratory muscles. *Id.*; *see*

also Letter from FDA to Elizabeth Barbehenn, *et al.* (Apr. 30, 2009), *available at* http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/UCM143989.pdf.

The FDA has approved Botox for therapeutic use in treatment of cervical dystonia (severe muscle spasms in the neck), strabismus (crossed eyes), blepharospasm (spasmodic blinking of the eyes), and primary axillary hyperhydrosis (excessive underarm sweating). *Id.* at 2. The FDA has also approved Botox for a single cosmetic use—treatment for temporary improvement of glabellar lines (wrinkles between the eyebrows). *Id.* Although Botox is used off label for treatment of limb spasticity (severe arm and leg muscle spasms), and for many cosmetic uses, *id.* at 11 & n.24, the FDA has not determined the overall safety and effectiveness for these uses, much less a safe dose. *Id.* at 16.

Strong evidence shows that injected botulinum toxin can spread throughout the body from the injection site, most commonly in therapeutic treatments (which typically require higher doses) but also in cosmetic use. *Id.* at 9-17. The spreading toxin can cause "serious adverse events" similar to severe botulism poisoning. *Id.* at 4, 10. In response to a Public Citizen petition, the FDA identified 225 case reports describing symptoms consistent with the effects of botulinum poisoning in a location of the body distant from the injection site, including cases involving hospitalization and death. *Id.* at 14. Importantly, the cases involving life-threatening or fatal reactions usually involved off-label uses of the toxin, such as treatment of children for spasticity associated with cerebral palsy. *Id.* at 4, 5, 12-13, 15 n.32, 16. As a result of Public Citizen's petition, the FDA recently required Allergan to add a warning to highlight the possibility of potentially life-threatening spread of the toxin from the injection site. *Id.* at 14.

The potentially deadly nature of Botox, especially for unapproved uses for which there is no evidence that the benefits outweigh the risks—including larger-than-approved doses and use in young children—highlights the importance of the current regulatory process. If this Court were to enjoin that process, Allergan could promote its drug for any off-label use, potentially even those for which the FDA has expressed safety concerns. The Court should reject Allergan's theory that the First Amendment provides a right to promote its drugs regardless of the impact on patients' health.

CONCLUSION

The defendants' motion for summary judgment should be granted and plaintiff's motion for a preliminary injunction should be denied.

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Respectfully submitted,

/s/ Gregory A. Beck
Gregory A. Beck (DC Bar # 494479)
Allison M. Zieve (DC Bar # 424786)
Public Citizen Litigation Group
1600 20th Street NW
Washington, DC 20009
202-588-1000

Counsel for Amicus Curiae Public Citizen